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FACIAL SELECTIVE DIELS-ALDER REACTIONS OF (1R,5R)-3-FORMYL-6,6-DIMETHYLBICYCLO[3.1.1]HEPT-3-EN-2-ONE

by

YANHONG LI

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta

Fall, 1993

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Supervisor

H. J. Liu

D. L. J. Clive

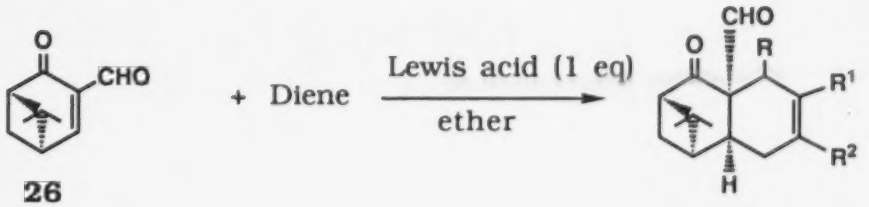
F. Pasutto

Date: September 14, 1993

Dedicated to my family

ABSTRACT

The stereofacially differentiated enone aldehyde **26** was chosen to study the effects of steric and electronic influence on the Diels-Alder reaction. Under Lewis acid catalysis, **26** adds to dienes at low temperatures at a reasonable rate. Yields of desired chiral adducts are good to high with zinc chloride and boron trifluoride etherate catalysis. In all cases, only products of addition to the *Re*-face of general type **33** were observed. The regiochemistry of the adducts is exclusively that predicted by the *ortho*- and *para*-rules. The stereochemistry shows a very high selectivity in favor of aldehyde-*endo* transition state products.



26 **33**

Some interesting by-products were also obtained. The mechanisms of these unexpected reactions are discussed.

The fact that the aldehyde group in the Diels-Alder adducts can be easily removed enhances the potential utility of the adducts in synthetic schemes.

ACKNOWLEDGEMENTS

I would like to express my sincerest gratitude to Professor H. J. Liu for his ever-willing support, guidance, and assistance throughout this work. His encouragement, patience and wisdom made all these years a lot more enjoyable. His interest and invaluable assistance in the preparation of this thesis are also greatly appreciated.

Thanks are also extended to excellent technical staff of the department. This work could not have been accomplished without their help: Dr. A. M. Hogg, L. Harrower, D. Morgan, J. Olekszyk and A. Jordan in the Mass Spectrometry Laboratory; R. Swindlehurst, D. Formanski, and J. Hoyle in the Spectral Services Laboratory; D. Mahlow and A Dunn in the Microanalytical Laboratory; Dr. T. T. Nakashima, T. Brisbane, G. Bigam, L. Kong and G. Aarts in the NMR Spectroscopy Laboratory; Dr. B. Santariero in the X-ray Laboratory, as well as all the personnel in the Electronic, Glass Blowing and Machine Shops. I would also like to thank the University of Alberta for financial support.

I wish to thank Ms. Judy Yip and Mr. Taiwei Ly for proof-reading part of the thesis.

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LIST OF ABBREVIATIONS

Ac	acetyl
APT	Attached Proton Test
ax	axial
Bn	benzyl
br.	broad
Bu	butyl
c.	concentration
CIMS	chemical ionization mass spectrum
d	doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
e	equatorial
eq	equivalent(s)
Eq.	Equation
Et	ethyl
gem	geminal
h	hour
HRMS	high resolution mass spectrum
i	iso
IR	infrared
m	multiplet
MCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minutes
MMPP	magnesium monoperoxyphthalate

m.p.	melting point
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Enhancement
p	*para*
Ph	phenyl
Py.	pyridine
q	quartet
r. t.	room temperature
t	tertiary
t	triplet
s	singlet
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TBDMS	*tert*-butyldimethylsilyl

INTRODUCTION

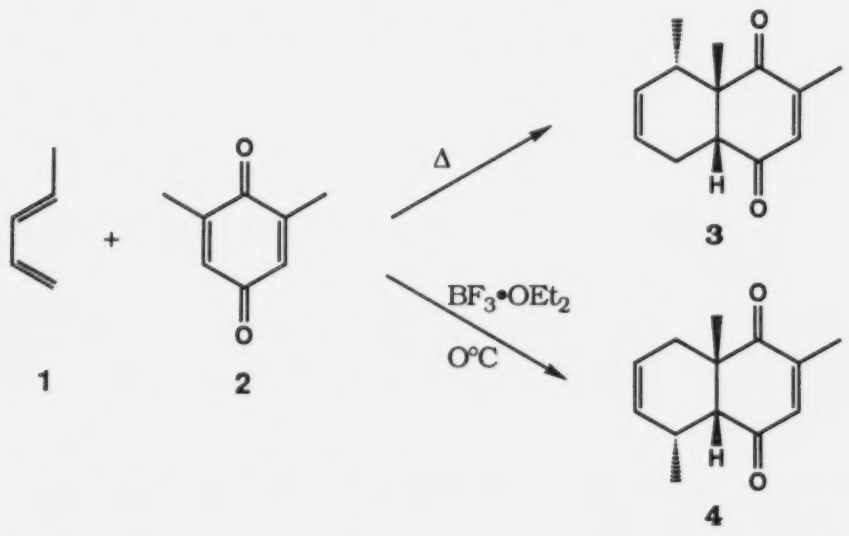
In the arsenal of the synthetic organic chemist, the Diels-Alder reaction occupies a position of particular prominence. A survey of carbon-carbon bond formation reactions reveals that, since its formulation in 1928,[1] this [4π + 2π] cycloaddition is one of the most widely used synthetic procedures, rivaling alkylation methods for ring formation.[2] This utility is enhanced by the formation of two bonds "simultaneously" with the introduction of up to four new asymmetric centers and its widespread application is also a consequence of good yields, mild reaction conditions, high stereoselectivity and predictability. Over the years, Diels-Alder reactions have been successfully applied as key steps in the construction of a variety of natural products, such as steroids,[3, 4] alkaloids[5,6] and prostaglandins.[7]

Although Diels-Alder reactions have been frequently used in organic synthesis, the detailed mechanism is still somewhat controversial, not only in the aspect of the reaction theory,[8-11] but also in other aspects of the reaction. The early development of a series of empirical rules by Alder and Stein[12] for predicting the structural outcome of Diels-Alder reactions greatly facilitated its use in organic synthesis. Yet they have been challenged by a number of growing facts and factors. For example, Diels-Alder additions of unsymmetrical dienes and dienophiles show a strong preference for the formation of specific regioisomers.[13-15] The regiochemistry of most of these cycloadditions

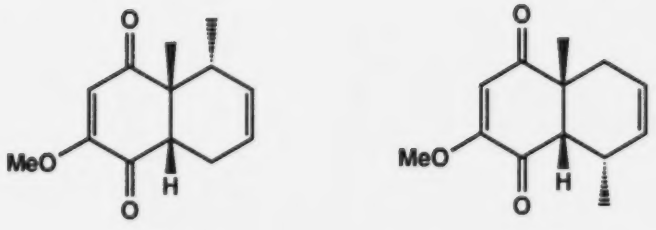
can be predicted by using a group of orientational rules (*ortho* and *para* rules). But, the reasons for these orientational effects have long been puzzling. When the "*meta*" adduct is dominant, the empirical rules are unable to predict what is going on. Since the late 60's, most investigators[16-19] have used the Frontier Molecular Orbital (FMO) approach to explain the experimental phenomena. In FMO theory, the regiochemistry is predicted from the primary interactions of frontier molecular orbitals and the coefficients of these orbitals. Using the same approach, Houk[20] predicted that when both the diene and dienophile are electron rich, the "*meta*" orientation would be favored. This has since been observed experimentally by Fleming *et al.*[21]

It has been found that Lewis acid catalysts can significantly influence the regio- and stereochemistry of Diels-Alder reactions so that the *ortho*-[22, 23] and *para*-selectivity[24-26] of the addition as well as the *endo*-selectivity[27-30] are greatly enhanced. A reversal of regioselectivity of Diels-Alder reaction induced by Lewis acid has also been reported by Valenta and coworkers as shown in Scheme 1.[31] Thus, the thermal reaction of *trans*-piperylene (**1**) with 2,6-dimethylbenzoquinone (**2**) afforded **3** while the boron trifluoride catalyzed reaction gave **4**. It had been previously assumed that in a Diels-Alder reaction, all the Lewis acids which enhance regioselectivity would increase the formation of the same regioisomer. It now appears that this is not the case and the orientation of the product may depend on the Lewis acid used.[32] As an example, the reaction of 2-methoxy-5-methylbenzoquinone with *trans*-piperylene at -16 °C using stannic chloride as a catalyst gave a 1:20 mixture of adducts **5** and **6**. In contrast, the same reaction catalyzed

by boron trifluoride afforded a 4:1 mixture of adducts **5** and **6**. These results have indicated that application of the previous empirical rules must be very cautious. One has to take all the factors involved in the Diels-Alder reaction into consideration.



Scheme 1

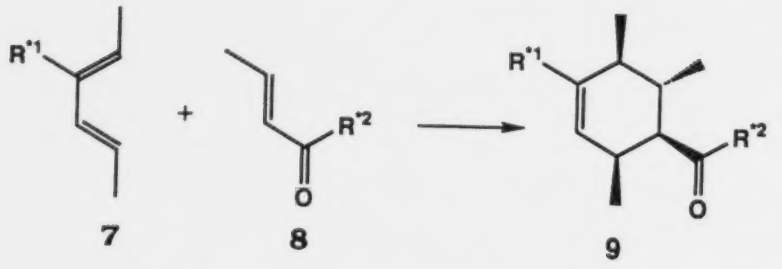


5 **6**

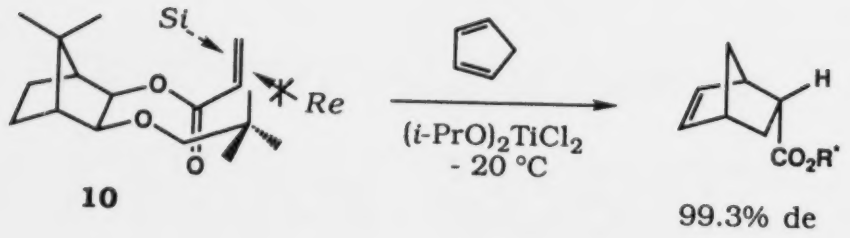
Lewis acids such as aluminum chloride, boron trifluoride and stannic chloride produce large increases in the rate of Diels-Alder reactions.[33] An outstanding example is the reaction of butadiene and methyl vinyl ketone. In one hour at room temperature in the presence of stannic

chloride, the reaction gave a 73% yield of 4-acetylcyclohexene. In the absence of a catalyst, adduct was not formed.[33] These discoveries have stimulated organic chemists to explore further the application as well as the mechanism of the versatile Diels-Alder reaction.

One of the most attractive features of the Diels-Alder reaction is its capability of generating up to four contiguous stereogenic centers in one synthetic operation. As discussed previously, the regio- and stereochemistry (*endo vs exo*) may be controlled by favorable orbital interactions. Another stereochemical feature, the π-facial diastereoselectivity which arises when the addends possess two different reactive faces, has attracted considerable attention recently. The asymmetric Diels-Alder reaction[34,35] pioneered by Wolborsky,[36,37] has been established as one of the most important tools in modern asymmetric synthesis. As illustrated in Equation 1, the reaction of two chiral components, diene **7** and dienophile **8**, can hypothetically produce 2^4 = 16 stereoisomers. However, potential stereoselection could be attained with the aid of the elements which govern the stereochemical course of the reaction, such as *cis*-addition, *endo*-addition and diastereofacial selectivity (orientation of diene and dienophile in the transition state). Most of the asymmetric Diels-Alder reactions involve optically active dienophiles[38-46] or dienes[47-49] which carry a removable chiral auxiliary group. As illustrated in Scheme 2, compounds **10-12** undergo Diels-Alder reaction in the presence of Lewis acid catalyst with excellent diastereoselectivity. They were devised in such a way that the chiral auxiliary group effectively blocked the *Re* face of the dienophile or diene.



(Eq. 1)



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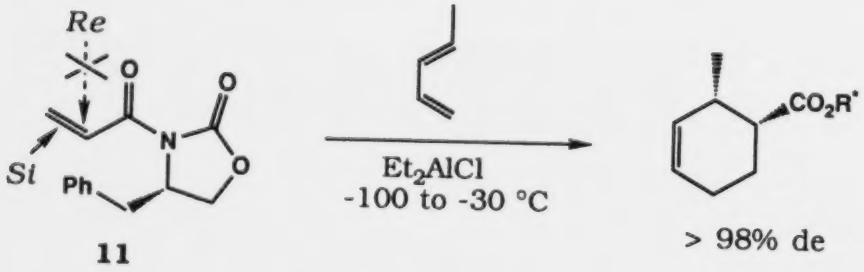

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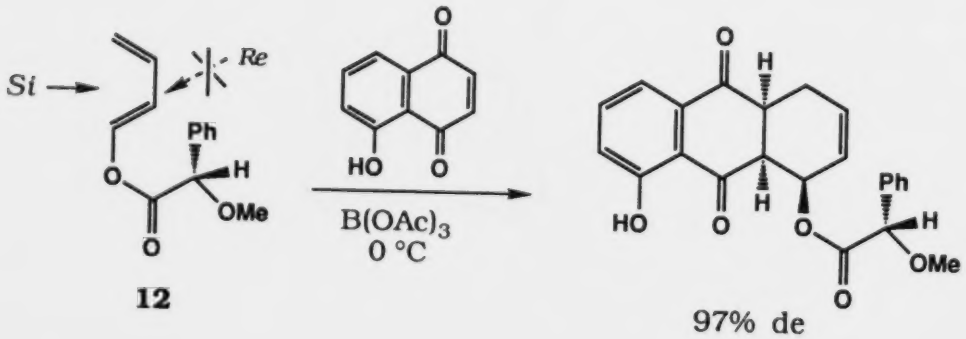

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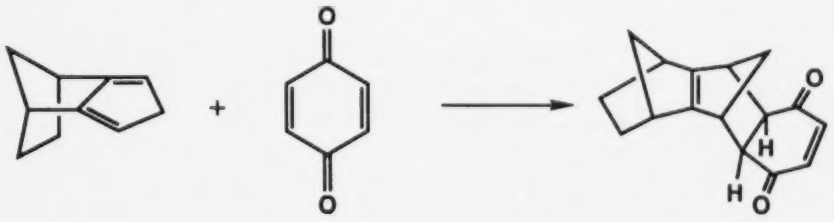
Scheme 2

In studies with isodicyclopentadiene and related compounds[50-55] (e.g., **13**), it was observed that dienophiles (e.g., **14**) reacted preferentially from the bottom face of the diene to give compounds such as **15** (Eq. 2). Paquette and coworkers[56] attributed the observed facial selectivity to the favorable σ/π interactions of the diene and the dienophile experienced in the transition state, while Houk and Brown[57] attributed the *endo* attack to torsional and steric effects. Clearly a delicate balance of many different factors influences the facial selectivity of these cycloadditions. Care must be taken in predicting the facial selectivity since one or many factors could play an important role in any of the cycloadditions.



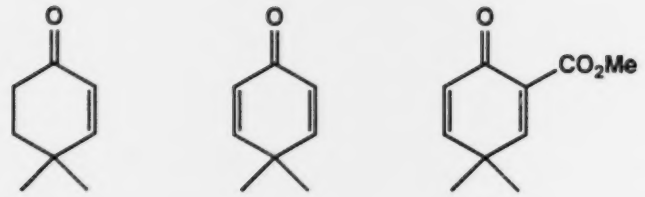
13 **14** **15** (Eq. 2)

Compared to the use of a covalently attached chiral auxiliary group, the use of a chiral catalyst appears to be a potentially more attractive method to induce asymmetric Diels-Alder reactions of prochiral dienes and dienophiles as two synthetic steps could be avoided. However, studies using Lewis acids such as menthoxyaluminium dichloride,[58] cyclohexanol derivatives of alkoxyaluminium dichloride,[59] $Eu(hfc)_3$,[60] acyloxyborane[61] and alkoxytitanium(IV) reagents[62,63] gave variable results. Among them only the chiral titanium reagents afforded asymmetric induction greater than 90%.

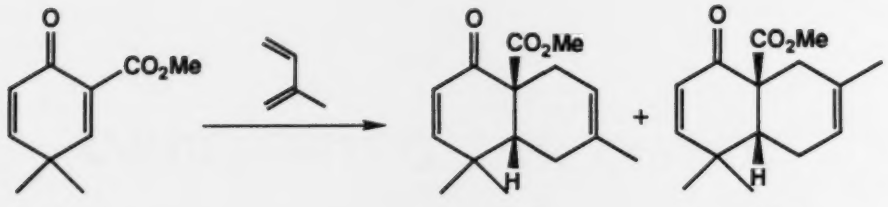
In principle, the addition of a 2-cyclohexenone to a substituted 1,3-butadiene, is a versatile approach to the decalin system. However, the thermal addition of dienes to cyclohexenones requires drastic conditions and usually produces low yields of the adducts.[64] In recent years, the use of Lewis acid catalysts has led to the utilization of specifically functionalized dienes and dienophiles to produce previously unattainable substitution patterns regio- and stereoselectively. Wenkert and coworkers[65-69] have made an extensive study of the Diels-Alder reaction of cycloalkenones using $AlCl_3$ as a catalyst. Liu and Browne[70-73] have carried out an extensive study of the Diels-Alder additions of 4,4-dimethyl-2-cyclohexenones **16-18**. It was observed that both the reaction rate and yield could be improved by the introduction of an additional electron-withdrawing group into the dienophilic moiety as predicted by Alder's rule.[74,75] It was also observed that the regiochemical outcome in the reaction of isoprene with dienone **18** could be affected by the use of different Lewis acids. Thus, the reaction of isoprene with dienone **18**[68] at room temperature using boron trifluoride as catalyst gave adducts **19** and **20** in a ratio of 30:70, while the same reaction catalyzed by stannic chloride produced an 82:18 ratio of adducts **19** and **20** (Scheme 3). The formation of the abnormal *anti-para* adduct **20** has been rationalized by a steric effect. Since boron trifluoride can only coordinate with one ligand, it preferentially complexes with the enone carbonyl. As a result, transition state **A** was favored. Since the *para*-rule guided addition **(19A)** promoted by the electron withdrawing effect on the dienophilic double bond was insufficient to counteract the steric directing effect which promoted *anti-para* addition **(20A)**, adduct **20** was

predominantly formed rather than **19.** In the case of $SnCl_4$, the Lewis acid is capable of forming a hexacoordinated complex with β-dicarbonyl compounds. In this complex (**21**) the electron withdrawing effect of the Lewis acid acting through both carbonyls, led to the formation of **19** as the major product *via* **19B**. This result has led to the further investigation of the effect of the double bond system.

Diels-Alder reaction of enone ester **22** with isoprene was carried out using three Lewis acid catalysts (BF_3·OEt_2, $SnCl_4$ and $FeCl_3$) and under a variety of reaction conditions.[76] In all cases, only the "*para*" product **23** was observed regardless of the conditions applied. These results implied that other than catalyst selection, a remote structural feature such as the cross-conjugated double bond in this dienophile system also played an important role in the regio- and stereochemical outcome of the Diels-Alder reaction. The difference in behavior of **22** from **18** under these reaction conditions arises from the less secondary orbital stabilization effect (through the interaction with the ketone carbonyl) in transition state **19A** due to the loss of C_5-C_6 double bond (in **18**) and its contribution to the whole cross-conjugated π-orbital system. Potential steric interaction between the quasi-axial proton of C_5 methylene of **22** and the diene would also contribute to the observed effect. Most likely, these two kinds of effects combine to eliminate completely any addition by type **A** (**19A** and **20A**) transition state.



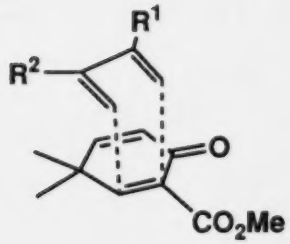
16 **17** **18**



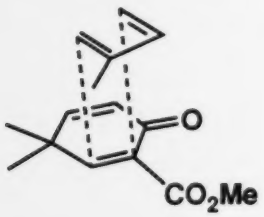
18 **19** **20**

$BF_3 \cdot OEt_2$	30 : 70
$SnCl_4$	82 : 18

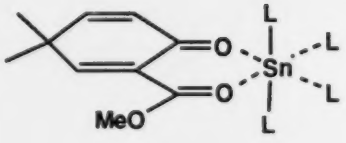
Scheme 3



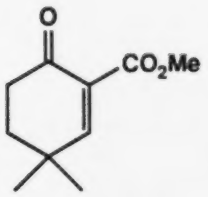
19A R^1=H, R^2=Me
20A R^1=Me, R^2=H



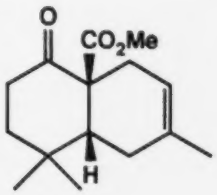
19B



21



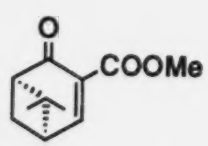
22



23

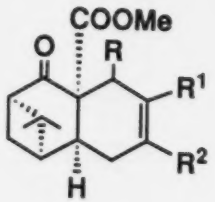
After examining the steric and electronic effects influencing the regiochemistry of Diels-Alder additions of enone ester **22**, our group became interested in the steric influence on the diastereofacial selectivity of Diels-Alder reaction of enones. The stereofacially differentiated dienophile **24** was chosen for this purpose. As shown in Table 1, in all cases, the addition took place exclusively from the less hindered *Si*-face (C_3 of **24**) to give adduct of general type **25** (Eq. 3) in good to high yields. The regiochemistry of adducts is exclusively that predicted by the *ortho*- and *para*-rules. The addition, wherever applicable, also shows a high degree of stereoselectivity in favor of the ester-*endo* transition state products.[77] This is likely due to the steric interaction between diene and the methylene bridge of the dienophile in the ketone-*endo* transition state.

Table 1. Lewis Acid Catalyzed Diels-Alder Additions of Enone Ester **24**



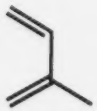
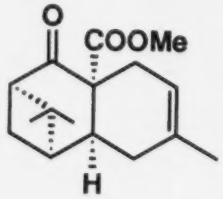
24

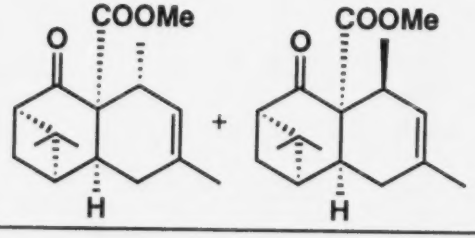
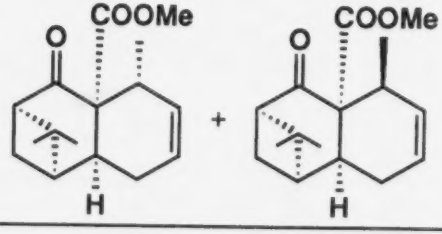
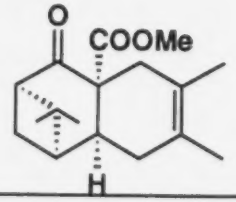
+ Diene $\xrightarrow[\text{ether}]{\text{Lewis acid (1eq)}}$

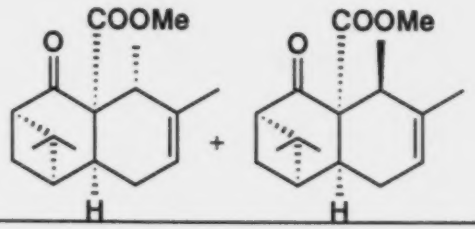
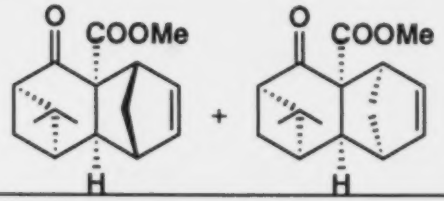


25

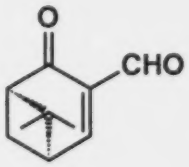
(Eq. 3)

Entry	Diene (eq)	Lewis acid	Temp. (°C)	Time (h)	Product(s)	(Ratio)	Yield (%)
1	 (20)	$BF_3{\cdot}OEt_2$	-10	12			29
2		$FeCl_3$	-20	2.75			34
3		$SnCl_4$	20	2			52
4		$SnCl_4$	-20	3			55
5		$SnCl_4$ (CH_2Cl_2)	-30	1.5			31
6		Et_2AlCl	-20	3			7
7		$ZnCl_2$	-20	21			95

8		$BF_3{\cdot}OEt_2$	0	4		(100:0)	16
9		$ZnCl_2$	-20	1.5		(88:12)	59
10	(10)	$ZnCl_2$	-40	24		(91:9)	100
11		$ZnCl_2$	-20	109		(86:14)	77
12		$ZnCl_2$ (2 eq)	-20	55		(100:0)	58
	(10)						
13		$ZnCl_2$	-20	41			93
	(20)						

14	(20)	$ZnCl_2$	-20	88		(81:19)	84
15	(20)	$ZnCl_2$	-20	61		(89:11)	53

Although the results of Diels-Alder reactions of enone ester **24** were rather good and the adducts proved to be synthetically useful,[77] we became interested in improving the stereoselectivity and synthetic utility by using enone aldehyde **26**. On one hand, a formyl group is stronger in electron-withdrawing and smaller in size than an ester group. Thus, the transition state should be even more in favor of *endo*-to-aldehyde due to the combined electronic and steric effects. On the other hand, the removal of a formyl group is expected to be much easier than the removal of an ester group in this case. The results of the investigation of Diels-Alder reactions of dienophile **26** are discussed in the next section.

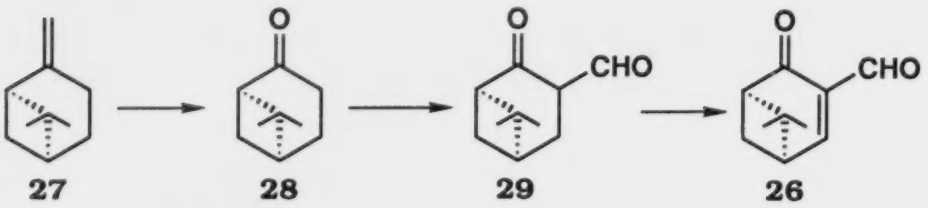


26

RESULTS AND DISCUSSION

I. PREPARATION OF DIENOPHILE 26

In order to prepare dienophile **26**, (-)-β-pinene (**27**) was chosen as a starting material since it has the same carbon skeleton as **26**. (-)-β-pinene has been used as an inexpensive, optically active starting material for asymmetric syntheses and the preparation of chiral reagents.[78-83] Enone aldehyde **26** was synthesized in high yield from **27** in three steps (Scheme 4).



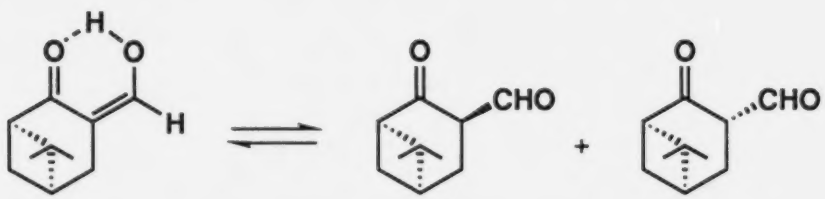
Scheme 4

Ozonolysis of (-)-β-pinene at -78 °C in a 1 : 1 mixture of dichloromethane-methanol followed by reductive workup with dimethyl sulfide gave (+)-nopinone (**28**) in 93% yield.[80] It was purified by flash column chromatography on silica gel. Its spectral data (IR, ^{1}H and ^{13}C NMR) are identical to those previously reported.[84] Problems in the synthesis of nopinone have been reported. In one case, the attempted purification of nopinone by vacuum distillation resulted in an explosion.[85] Similarly, allowing the concentrated

reduction mixture to warm up from 0 °C to room temperature also resulted in a violent explosion.[86] We repeated the preparation several times and carried out vacuum distillation once, instead of chromatography for purification without incident. The problems reported might be due to the incomplete reduction of the ozonolysis products or improper handling of the workup procedure. The following are some important points for this reaction: (i) A persistent blue or purple colour of the reaction solution can not serve as an indication of the completion of ozonolysis. We found that even when the purple colour remained, there was still a lot of starting material present in the reaction mixture. At that point, only about 78% yield of product was formed.[84] On the other hand, when TLC analysis showed the disappearance of the starting material, a 93% isolation yield of **28** was achieved. (ii) After the ozonolysis was completed, oxygen gas must be blown through the reaction mixture (5-10 min) to remove the excess of ozone. (iii) The reducing agent (Me_2S) must be added at low temperature (-78 °C) and then the reaction mixture should be allowed to warm up slowly (during a period of 2-4 h) to room temperature, instead of the reverse order. (iv) The amount of the reducing agent should be in excess and the reduction time should be sufficiently long (overnight) to ensure the completion of the reaction.

The formyl group was introduced by treating **28** with sodium hydride and ethyl formate in THF under an argon atmosphere. The reaction was catalyzed by a few drops of ethanol and proceeded smoothly at room temperature. After 3 h, keto aldehyde **29** was obtained in 96% yield.[87] Its IR spectrum showed carbonyl bands at 1725 cm^{-1} (for a

saturated CHO), 1713 cm^{-1} (for a saturated C=O) and 1653 cm^{-1} (for a chelated β-hydroxy-α,β-unsaturated ketone carbonyl). It also displayed absorptions at 3400-3130 cm^{-1} (a broad shoulder for OH) and 1598 cm^{-1} (C=C) which indicated the presence of an enol moiety in the molecule. The ^{1}H NMR spectrum supported this structural feature by showing two broad singlets, one at δ 13.35 for the chelated enol O**H** and the other at δ 7.18 for the enol double bond proton. The singlets in the ^{13}C NMR APT spectrum at δ 209.45, 163.92 and 107.16 confirmed that **29A** was present as the major component. Other minor ^{1}H NMR signals, like singlets at δ 9.65 and 9.40 (for the C**H**O in **29B** and **29C**, but we are not sure which is which), and the presence of three pairs of singlets (for the *gem*-dimethyl groups) indicated that compound **29** was a mixture of its tautomer and epimers (7:2.5:1). The ratio of these three components was not constant. It varied as the state of the compound changed, for instance, in pure form or in solutions of different solvents or at different temperatures.



29A **29B** **29C**

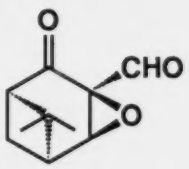
The dehydrogenation of **29** was carried out in two steps, phenylselenenylation followed by oxidative elimination of the resulting selenide.[88]

Pyridine was added to a solution of phenylselenenyl chloride (PhSeCl) in dichloromethane at 0 °C under an argon atmosphere. The colour of the solution changed from dark red to yellow-brown and a white fume was generated at the same time. This might be due to the formation of a PhSeCl-Py complex.[89] The complex activated PhSeCl in the reaction. After 10 min, a solution of **29** in methylene chloride was added. At the end of the addition which took about 3 min, an instant colour change from yellow-brown to bright yellow occurred, indicating the completion of the selenenylation reaction. TLC analysis confirmed that starting material was absent.

Extensive efforts were made in order to improve the oxidative elimination process. After washing the selenenylation reaction mixture with water to remove pyridinium chloride, the remaining selenide was oxidized with 30% aqueous hydrogen peroxide solution to give the enone aldehyde **26** in 70% yield. This compound showed carbonyl bands in its IR spectrum at 1724 and 1691 cm^{-1} and double bond adsorption at 1593 cm^{-1}, which are characteristic of an α-formyl α,β-unsaturated ketone. The ^{1}H NMR spectrum showed a singlet at δ 10.00 for the aldehydic proton and a doublet of doublets at δ 8.31 for the vinylic proton. The presence of a conjugated double bond was confirmed by signals at δ 165.42 and 132.25 in the ^{13}C NMR APT spectrum.

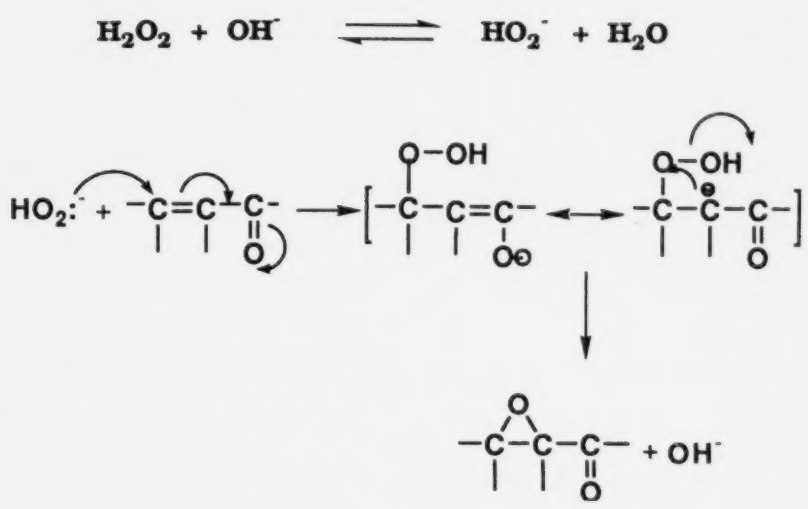
However, the above reaction conditions were unable to produce pure compound **26**. It was always accompanied by epoxide **30** as a result of

over oxidation. It was found that the epoxidation was very sensitive to the acidity of the reaction media. When the oxidation was carried out under neutral conditions, the amount of epoxide increased rapidly and it even became the major product (compound **26**:**30** = 1:1.2). When the selenide solution was oxidized directly after washing with 1 N hydrochloric acid, only a small amount of epoxide was formed (**26**:**30** = 8:1).



30

How the epoxidation happened remains unclear. The widely accepted mechanism for the epoxidation of an α,β-unsaturated ketone or aldehyde by hydrogen peroxide (shown in Scheme 5)[90-92] does not fit in this case very well. In that mechanism, hydroperoxide ion (HOO^-) acts as a nucleophile to attack the conjugated double bond. Therefore, an alkaline media is essential to deprotonate hydrogen peroxide to generate HOO^-. In the present case, there was no alkaline media present. If any HOO^- existed, it must have come from the self-dissociation of hydrogen peroxide (Eq. 4).[93] Such a process would not be efficient to induce epoxidation of a normal α,β-unsaturated ketone or aldehyde. For compound **26**, however, the double bond is doubly activated and thus highly reactive towards Michael addition. It is possible that any amount of HOO^- is sufficient to initiate rapid epoxidation.



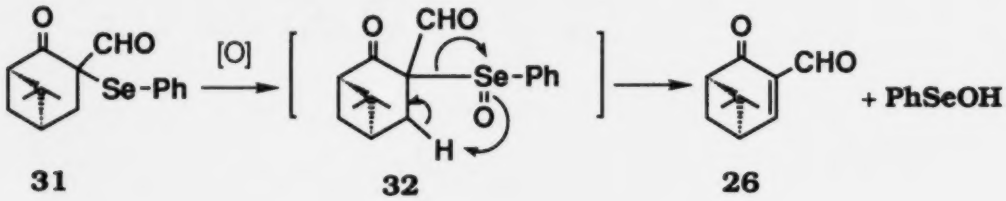
Scheme 5

$H_2O_2 \rightleftharpoons HOO^- + H^+$ (K = 0.67 x 10^{-12} at 0 °C) (Eq. 4)

This could, somewhat, explain the above experimental results. Under neutral conditions, once the epoxidation is initiated by a trace amount of HOO^-, then the epoxidation could be catalyzed by the OH^- generated in the reaction itself. This process could make the epoxide **30** become the major product. However, when the reaction was carried out under acidic conditions, the hydroxide generated was neutralized. Therefore, the above discussed epoxidation process was slowed down and epoxide **30** turned out to be the minor product.

Recently, Reich suggested another possible mechanism for the oxidation step.[94] In his opinion, the rate of oxidation of the selenide to the selenoxide by hydrogen peroxide is relatively slow. The

observed rapid oxidation rate is attributed to perseleninic acid ($PhSeO_3H$) which is generated during the reaction as shown in Scheme 6.[95] It is perseleninic acid that acts as the true oxidant which enables the reaction to proceed at the fast rate that was observed. This proposal is reasonable since perseleninic acid is a very strong oxidant. If this is true, it is possible to make the oxidation go faster by adding seleninic acid into the reaction mixture as a catalyst at the beginning of the reaction. If this can make the oxidation proceed faster than the subsequent epoxidation, a higher yield of the desired product may be achieved. In light of this rationalization, a couple of reactions were carried out involving seleninic acid as a reagent. The results are listed in Table 2.



31 **32** **26**

$$\mathbf{3\ PhSeOH \longrightarrow PhSeO_2H + Ph\text{-}Se\text{-}Se\text{-}Ph + H_2O}$$

$$\mathbf{PhSeO_2H + H_2O_2 \longrightarrow PhSeO_3H + H_2O}$$

Scheme 6

Table 2. The results of oxidation of the selenide in the presence of [22] $PhSeO_2H$

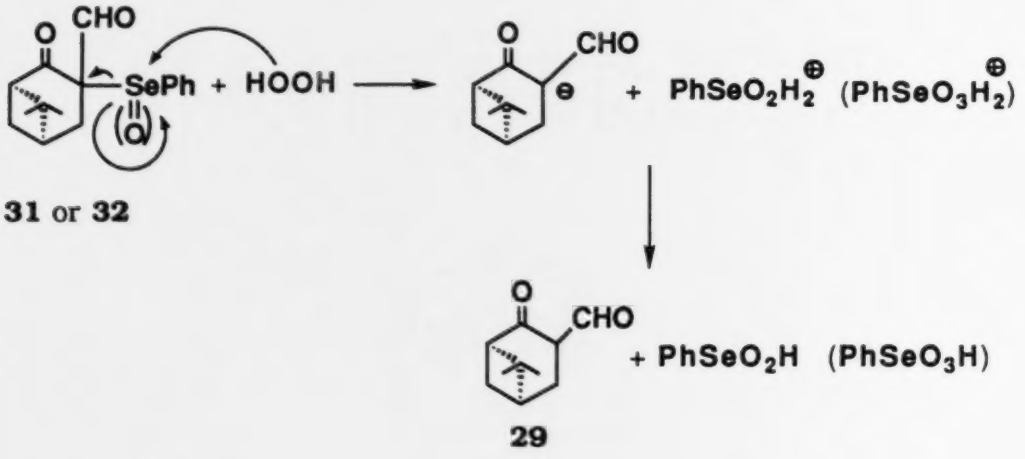
	with $PhSeO_2H$				Blank		
Entry	$PhSeO_2H$ (eq)	Time (min)	Yield (%)	Ratio (**26**:**30**)	Time (min)	Yield (%)	Ratio (**26**:**30**)
1	0.1	60	65	8:1	120	66	7:1
2	0.5	35	67	5:1	100	61	7:1

We did observe a significant increase in the reaction rate, but no obvious improvement of the yield or the ratio of the two compounds. It is conceivable that the peracid catalyzed both the oxidation and the epoxidation and the rates of both reactions increased to about the same extent. Thus, we could only observe the rate inhancement but not the change in ratio. In fact, when 0.5 eq of $PhSeO_2H$ was used, the ratio of the two products dropped to 5:1 (Table 2, entry 2). Presumably, in this case, excessive peracid reacted with the desired product **26** to form the undesired epoxide **30**. Of many runs, the best ratio obtained for **26** and **30** was 12:1 after purification by bulb-to-bulb distillation.

Compounds **26** and **30** were not separable by either column chromatography or bulb-to-bulb distillation. Pure epoxide **30** was recovered after the subsequent Diels-Alder reaction, in which enone aldehyde **26** was totally consumed. Epoxide **30** displayed a singlet at δ 9.65 for the aldehydic proton and a doublet at δ 3.89 for the proton attched to the epoxy ring in the ^1H NMR spectrum. The IR spectrum

showed absorptions at 1741 (CHO) and 1710 (C=O) cm^{-1}. HRMS showed m+1/z at 181.0863.

Another process occurred during the oxidation. A small amount (3-8%) of **29** was always recovered. Selenide **31** and Selenoxide **32** are both very congested at the C_3 position and therefore are not stable. Attacked by a nucleophile, such as hydrogen peroxide, at the selenium atom could result in the formation of **29** *via* the pathway shown in Scheme 7.



Scheme 7

Other methods attempted to improve the production of enone aldehyde **26** included DDQ oxidation of **29** and the use of other oxidants instead of hydrogen peroxide for oxidative elimination of selenide **31**. An examination of the results listed in Table 3 reveals that these procedures were far inferior.

Table 3. The results of other methods tried for the preparation of **26**

Method or oxidant	Result	Reference
DDQ	unknown product	96
O_3	3%	95
$NaIO_4$	no product	95
MMPP	no product	97
H_2O_2-THF	no product	95
Non-oxidative elimination	decomposition	89

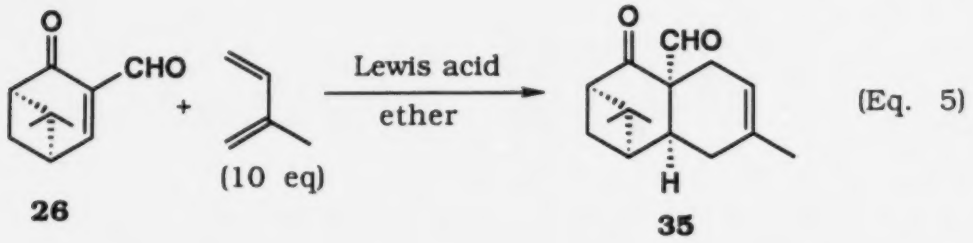
II. DIELS-ALDER REACTIONS OF DIENOPHILE 26

After we had enone aldehyde **26** in hand, a variety of Lewis acids and conditions were explored for its Diels-Alder reaction with isoprene. The results of these investigations are listed in Table 4.

The particular Lewis acids were chosen because they were previously noted as suitable catalysts for related cross-conjugated enone dienophiles.[98,99] In the present case, it was found that the Diels-Alder reaction was very sensitive to the acidity of the Lewis acid catalyst. The results showed that the milder the Lewis acid catalyst, the better the yield. Good yields were obtained with $ZnCl_2$ as a catalyst. Boron trifluoride is a very strong Lewis acid. But when it coordinates with ether, the resulting etherate becomes a weak Lewis acid. When $FeCl_3$ and $SnCl_4$ were used, the yields dropped drastically. These phenomena may be the result of greater stability of the strained ring

system of the reactant and the products to the relatively mild acidic conditions of boron trifluoride etherate and zinc chloride catalyses than the stronger Lewis acids examined.

Table 4. Lewis acid catalyzed Diels-Alder addition of isoprene to enone aldehyde **26**

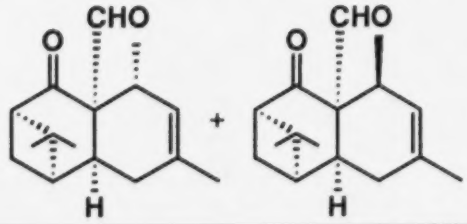
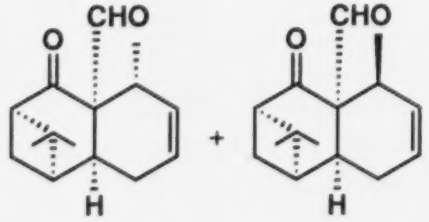


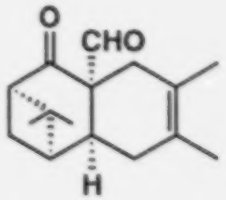
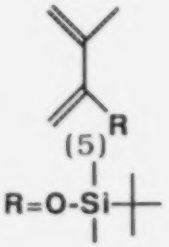
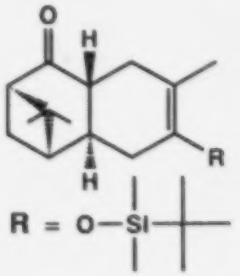
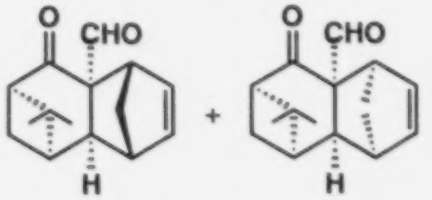
26 **35** (Eq. 5)

Lewis acid(eq)	Temp (°C)	Time (h)	Yield (%)
$ZnCl_2$ (2.0)	-20	18	74
$ZnCl_2$ (1.0)	-20	18	71
$ZnCl_2$ (1.0)	-20 + r.t.	15 + 2	72
$SnCl_4$ (1.0)	-20	6	0
$FeCl_3$ (1.0)	-20	1	19
$BF_3{\cdot}OEt_2$ (1.0)	-20	2	84

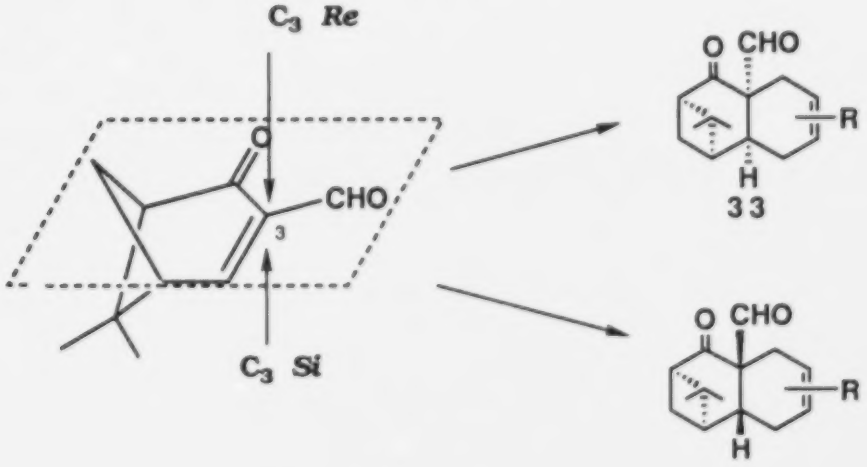
In further investigations of the scope of the Diels-Alder reaction of **26**, boron trifluoride etherate and zinc chloride were used as Lewis acid catalysts. Adducts were obtained in good to high yields. Results are summarized in Table 5.

Table 5. Diels-Alder additions of dienes to enone aldehyde **26**

Entry	Diene (eq)	Lewis acid (1 eq)	Temp. (°C)	Time (h)	Product(s)	(Ratio)	Yield (%)
1	(10)	$BF_3 \cdot OEt_2$	-40	3		(133:1)	82
2	(10)	$ZnCl_2$	-20	16		(170:1)	60
3		$BF_3 \cdot OEt_2$	-20	1		(64:1)	71

4	(10)	$BF_3 \cdot OEt_2$	-20	1.5		92
5	 (10) (5) R=O-Si	$ZnCl_2$	-20	4		70
6		$ZnCl_2$	-40--> -15	3.5 1.5		68
7	(10)	$BF_3 \cdot OEt_2$	-20	1.5		0
8		$BF_3 \cdot OEt_2$	-40	0.5		0
9		$ZnCl_2$	-20	4	(20:1)	52

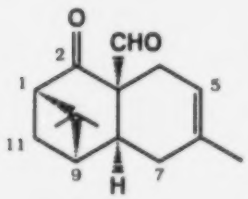
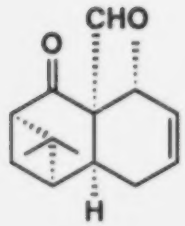
The zinc chloride used in the Diels-Alder reactions was flame dried under vacuum, before dissolving it in ether to make a clear solution. Enone aldehyde **26** in ether was added to the zinc chloride solution at room temperature and a thick pale yellow precipitate formed. The formation of this precipitate was probably due to the formation of a complex between zinc chloride and **26**. After a few minutes, the precipitate stuck onto the wall of the round bottomed flask and the solution became clear again. Then the reaction mixture was cooled to -20 °C and the diene was added. The experimental procedures were slightly altered when the other catalysts ($BF_3{\cdot}OEt_2$, $FeCl_3$, $SnCl_4$) were used. Both the catalyst and the diene were added to a solution of **26** at the stated temperature. When boron trifluoride etherate was added to the solution of **26**, precipitate was not formed. Instead, the reaction mixture was slightly cloudy, but became clear after 30 min.

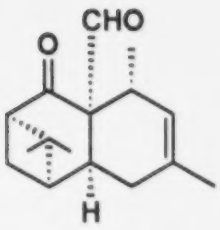
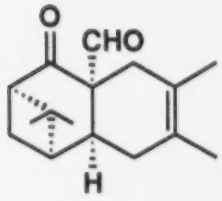
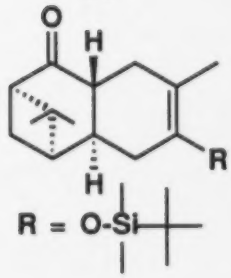
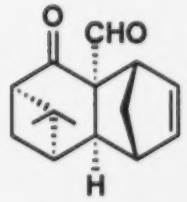


Scheme 8

In principle, Diels-Alder addition to enone aldehyde **26** could occur from either the sterically more hindered *Si*-face or the less hindered *Re*-face to give stereochemically distinct products. In all cases, only the products of the addition to the *Re*-face of general type **33** were obtained (Scheme 8). The *gem*-dimethyl group in **26** served to direct the Diels-Alder addition to the less hindered *Re*-face, as indicated by the stereochemistry of the ring junction of the adducts listed in Table 5. The structures of the adducts were established by using spectroscopic methods including ^1H NMR, ^1H decoupling and NOE experiments. The results of the NOE experiments are summarized in Table 6.

Table 6. NOE data for Diels-Alder adducts

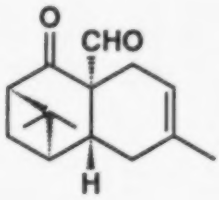
Compound	Irradiation	δ (ppm)	% Enhancement (H)
 **35**	H_8	2.94	3.7 (CHO), 2.7 (*endo* CH_3)
	exo CH_3	1.32	4.7 (*endo* CH_3), 14.5 (H_1), 17.7 (H_{11}*exo*), 18.4 (H_9)
	C_6-CH_3	1.74	9.2 (H_5), 16.0 (H_7)
 **37**	H_8	2.80	4.8 (H_7), 3.9 (H_9), 5.8 (*endo* CH_3)
	endo CH_3	0.71	4.8 (*exo* CH_3), 7.0 (H_8)
	C_4-CH_3	1.40	9.7 (CHO), 9.8 (H_5), 9.3 (H_4)

 **42**	H_8	2.82	5.8 (*endo* CH_3)
	C_4-CH_3	1.40	5.3 (H_5), 6.4 (CHO), 5.9 (H_4)
 **44**	*endo* CH_3	0.71	3.7 (CHO), 5.3 (H_8), 4.9 (*exo* CH_3)
 **46**	*exo* CH_3	0.89	16.5 (H_1), 10.2 (H_9), 13.0 (H_{11}*exo*)
	C_5-CH_3	1.43	5.6 (H_4), 2.8 (Si-CH_3)
 **50**	*endo* CH_3	0.75	2.3 (CHO), 8.2 (*exo* CH_3), 6.8 (H_8)

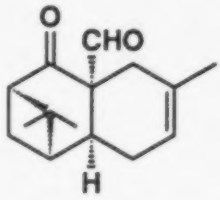
A. Addition to isoprene

The reaction of an ethereal solution of enone aldehyde **26** with isoprene under zinc chloride catalysis gave the adduct in 74% yield after 18 h. When boron trifluoride etherate was used as a catalyst, the reaction was rapid. It was finished in 2 h with a 84% yield of the

adduct. The adduct displayed a set of 15 lines in the ^{13}C NMR APT spectrum with 7 lines in phase to the deuteriochloroform signals and 8 lines antiphase, indicating the presence of a single compound. This compound had a specific rotation ($[\alpha]^{23}_D$) of -115.9° (c. 0.75, $CHCl_3$). The mass spectrum showed a molecular ion peak at m/z 232.1462 consistent with the chemical formula $C_{15}H_{20}O_2$. The IR spectrum showed carbonyl bands at 1730 (CHO) and 1698 (C=O) cm^{-1}. Its ^1H NMR spectrum displayed a multiplet at δ 5.33 for the vinylic proton, a singlet at δ 9.70 for the formyl group and three methyl singlets at δ 1.74 (vinylic), 1.32 and 0.73 (*gem* CH_3's).



35



36

Structure **35** could be assigned to the adduct, if the Diels-Alder addition followed the normal *para*-rule. However, orientational reversal in violation of the *para*-rule in the Diels-Alder reaction of a 2-substituted diene has been observed.[68] It was therefore possible that the addition of isoprene to **26** could produce the regioisomer **36**. To rule out this possibility, extensive ^1H decoupling experiments were carried out and all the protons of the adduct were assigned. The ^1H NMR assignments for this compound are summarized in Table 7. A doublet of doublets, H_{4e}, was observed to couple to H_5 with a coupling constant of 7.0 Hz in accord with the $CH_3C{=}CH_xCH_yH$ system (J_{xy} = 4-10.0 Hz). On the other hand, the regioisomeric adduct would be

expected to show a smaller coupling constant for the [32] $CH_x=C(CH_3)CH_yH$ system (J_{xy} = 0-3 Hz).[100] Clearly, the ^1H NMR spectral data are consistent with structure **35** for the Diels-Alder adduct.

Table 7. ^1H NMR data for adduct **35**

Proton	Chemical shift (δ ppm)	Multiplicity (J in Hz)
H_1	2.61	dd (5.5, 5.5)
H_{4e}	2.83	dd (16.0, 7.0)
H_{4ax}	2.22	dddd (16.0, 8.0, 2.5, 2.5)
H_5	5.33	m
H_{7e}	2.15	m
H_{7ax}	1.91	m
H_8	2.94	dddd (10.0, 7.5, 2.0, 2.0)
H_9	2.15	m
H_{11exo}	2.52	dddd (11.0, 8.5, 5.5, 2.0)
H_{11endo}	1.89	d (11.0)
vinylic CH_3	1.74	br s
exo CH_3	1.32	s
endo CH_3	0.73	s
CHO	9.7	s

The stereochemistry of the ring junction was determined by NOE experiments. Irradiation of the proton H_8 signal at δ 2.94 resulted in 3.7% and 2.7% enhancements on the formyl and the methyl at δ 0.73, respectively. This implied that H_8 and CHO were on the same face, as

well as the *gem*-dimethyl group. Therefore, the addition of isoprene obeyed the *cis*-principle and was to the *Re*-face of **26** to give adduct **35** with α-H_8. When the methyl at δ 1.32 was irradiated, NOE enhancements of 14.5% on H_1, 17.7% on H_{11exo}, 18.4% on H_9 and 4.7% on methyl at δ 0.73 were observed. From these NOE experiments, the *gem*-dimethyl and the *exo* and *endo* protons of the methylene bridge could be assigned. The appearance of the *exo* methyl signal further down field than the *endo* methyl signal is probably due to the shielding of the *endo* methyl by the ketone carbonyl. The H_{11exo} at δ 2.52 with a dddd multiplicity, was coupled to H_1 (J = 5.5 Hz), H_9 (J = 8.5 Hz), H_{11endo} (J = 11.0 Hz) and H_8 (W-coupling, J = 2.0 Hz). On the other hand, H_{11endo}, which was strongly shielded relative to H_{11exo}, appeared as a readily recognizable doublet (J = 11.0 Hz) as the dihedral angles of H_{11endo} to H_1 and H_9 were about 90° each.

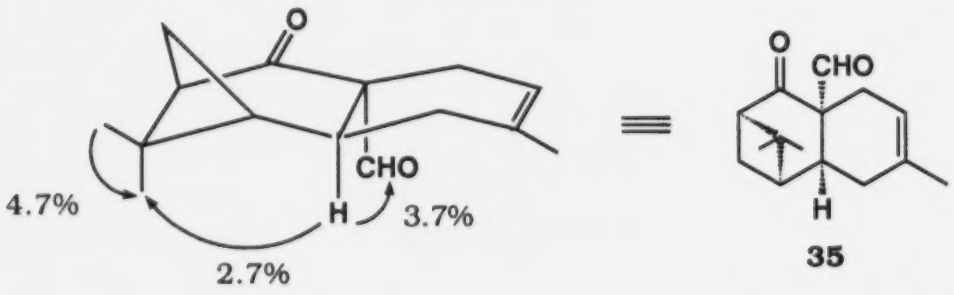
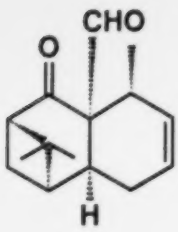


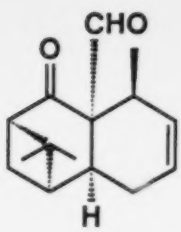
Figure 1. NOE data for adduct 35

B. Addition to *trans*-piperylene

When an ethereal solution of enone aldehyde **26** was reacted with *trans*-piperylene at -20 °C under zinc chloride catalysis, two adducts in a ratio of 170:1 were obtained in 60% yield. In the case of boron trifluoride etherate catalysis, two adducts in a ratio of 64:1 were formed in 71% yield. In both cases, the adducts showed only one spot on the TLC plate and could not be separated by flash chromatography on silica gel. The adducts displayed two sets of signals in the ^{13}C NMR APT spectrum as well as in the ^{1}H NMR spectrum. Since the product obtained was a mixture of two inseparable diastereomers, the specific rotation was not measured. The adducts showed a molecular ion peak at m/z 232.1441 which was in agreement with the formula $C_{15}H_{20}O_2$. The IR spectrum exhibited strong absorptions at 1723 and 1693 cm^{-1}, indicating the presence of an aldehyde and a ketone function respectively. The ^{1}H NMR spectrum displayed two CHO signals at δ 10.04 and 9.63, two pairs of vinylic protons at δ 6.00 (ddd), 5.42 (ddd) and 6.00 (m), 5.75 (dddd), two sets of methyl singlets at δ 1.31, 0.71 (*gem*) and 1.32, 0.66 (*gem*) along with two methyl doublets at δ 1.40 and 1.05, for the major and minor isomers respectively. In the ^{13}C NMR APT spectrum, two carbonyl carbons appeared at δ 211.0 (C=O), and 204.27 (CHO) for the major isomer. The minor isomer was too small in quantity to show up in the ^{13}C NMR APT spectrum for carbonyl carbons.



37



38

If the Diels-Alder reaction obeyed the normal *ortho*-rule, then the structures of the adducts could tentatively be assigned as **37** and **38**. To determine conclusively the regiochemistry of the adducts, extensive ^1H decoupling experiments were carried out on the major isomer and a complete spectral assignment was achieved (Table 8). The ring junction proton (H_8), which appeared as a dddd at δ 2.80, was coupled to H_{7ax} (J = 10.5 Hz), H_{7e} (J = 7.5 Hz), H_9 (J = 2.0 Hz) and H_{11exo} (W-coupling, J = 2.0 Hz). This coupling pattern indicated that two hydrogen atoms were attached to C_7. This feature was also observed for adduct **35**, in which there was no substituent at C_7. Thus, the methyl substituent could only be located at C_4 and the major isomer must possess the regiochemistry as depicted in structure **37**.

Table 8. ^1H NMR data for adduct **37**

Proton	Chemical shift (δ ppm)	Multiplicity (J in Hz)
H_1	2.62	dd (5.5, 5.5)
H_4	2.58	m
H_5	5.42	ddd (9.5, 3.0, 3.0)
H_6	6.00	m
H_{7e}	2.34	ddd (15.0, 7.5, 7.5)

H_{7ax}	1.85	m
H_8	2.80	dddd (10.5, 7.5, 2.0, 2.0)
H_9	2.10	ddd (5.5, 5.5, 2.0)
H_{11exo}	2.48	dddd (11.0, 5.5, 5.5, 2.0)
H_{11endo}	1.89	d (11.0)
C_4-CH_3	1.40	d (7.5)
exo CH_3	1.31	s
endo CH_3	0.71	s
CHO	10.04	s

The stereochemistry of **37** was determined by NOE experiments. Irradiation of the *endo*-methyl resulted in an NOE enhancement of 7.0% for H_8. According to the *cis*-principle, CHO group should be on the same face as H_8. This indicated that the addition of *trans*-piperylene occurred from the *Re*-face. Saturation of the methyl doublet (δ 1.40) produced a 9.7% enhancement on CHO (see Figure 2). Evidently, the C_4-methyl is on the same face as the aldehyde group. These experiments conclusively established the stereochemistry of the major adduct as **37**.

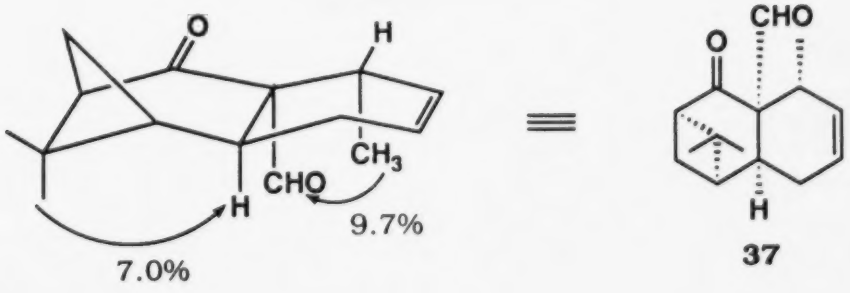
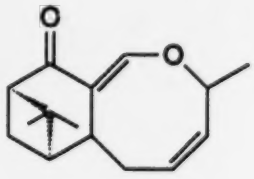


Figure 2. NOE data for adduct 37

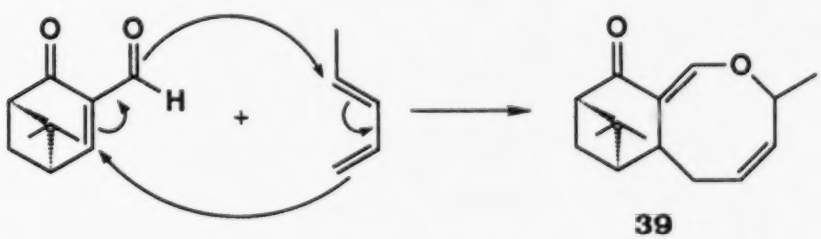
The presence of a trace amount of a minor isomer could only be detected by high resolution NMR techniques. Some ^{1}H NMR signals of the minor isomer were separated from those of the major isomer. The rest were buried under the signals of the major isomer. Therefore, NOE and decoupling experiments were not performed on the minor adduct. It was impossible to complete all the spectral assignments. Compared to previous results obtained from our group[84], the two adducts should be epimers. Thus, the minor isomer was tentatively assigned structure **38**.



39

Other than adducts **37** and **38**, there was an unexpected product formed during the Diels-Alder reaction between enone aldehyde **26** and *trans*-piperylene, with either boron trifluoride etherate or zinc chloride catalysis, in 14% and 15% isolated yield, respectively. This compound showed an intense spot under the UV lamp (short wavelength) on a TLC plate and a greater polarity than the Diels-Alder adducts. It was isolated as a white crystalline compound after column chromatography. It displayed 15 carbon signals in the ^{13}C NMR APT spectrum with 5 lines in phase to the $CDCl_3$ signals and 10 lines antiphase, indicating the presence of a single compound. The mass spectrum showed a molecular ion peak at m/z 232.1462, in

agreement with the formula, $C_{15}H_{20}O_2$, isomeric with the desired adducts. However, the IR spectrum showed only one carbonyl absorption at 1684 cm^{-1}, which along with a band at 1602 cm^{-1} (for a double bond) indicated the presence of a conjugated enone moiety in the molecule. The CHO signal was no longer in existence in the ^1H NMR spectrum. Instead, there was a broad singlet at δ 7.40, typical for a proton attached to a double bond of an enolic system. It also displayed two dddd signals at δ 5.82 and 5.53 for vinylic protons. Another dddd signal appeared at δ 4.59 attributable to a proton adjacent to an oxygen atom. Two methyl singlets were observed at δ 1.35 and 0.95 (*gem* CH_3's). According to the spectral data, structure **39** was assigned to the unexpected product, which was formed *via* a 1,4-cyclization process instead of a Diels-Alder reaction (see Scheme 9). The coordination between the dienophile and the catalyst made the already highly reactive double bond even more accessible to nucleophilic attack.

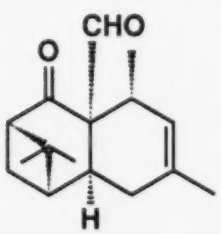


39

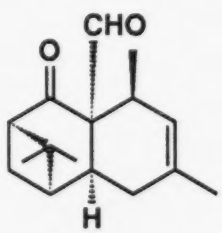
Scheme 9

C. Addition to *trans*-2-methyl-1,3-pentadiene

At -40 °C, the boron trifluoride etherate catalyzed Diels-Alder reaction of enone aldehyde **26** with *trans*-2-methyl-1,3-pentadiene proceeded smoothly to give a 82% yield of a colourless liquid. The mass spectrum showed a molecular ion peak at m/z 246.1619, which was consistent with the formula $C_{16}H_{22}O_2$. The IR spectrum showed carbonyl bands at 1713 (CHO) and 1694 (C=O) cm^{-1}. Although the products showed only one spot on TLC and could not be separated by flash chromatography on silica gel, the ^1H NMR spectrum indicated the presence of two compounds in a ratio of 133:1. The mixture displayed two formyl singlets at δ 10.04 and 9.63, two vinylic proton multiplets at δ 5.08 and 5.37, two broad vinylic methyl singlets at δ 1.78 and 1.73, and two sets of *gem*-dimethyl singlets at δ 1.32, 0.66 and 1.33, 1.02, for the major and minor isomers, respectively. The presence of two isomers was confirmed by the signals for doubly bonded carbons at δ 138.47, 124.58 (for the major isomer) and 129.40, 123.60 (for the minor isomer) in the ^{13}C NMR spectrum, which also showed carbonyl signals at δ 211.90 (C=O) and 204.23 (CHO) for the major isomer.



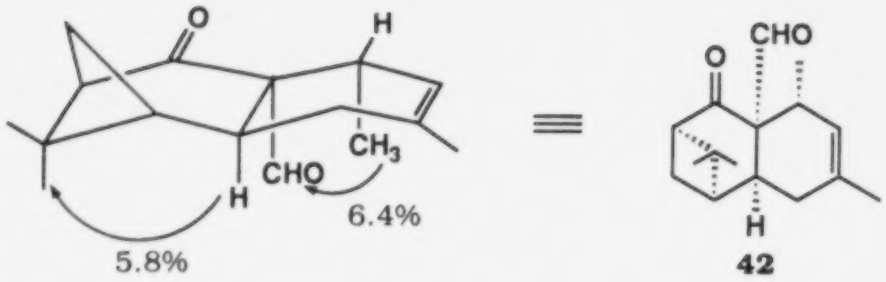
42



43

On the basis that the Diels-Alder reaction followed the normal *ortho*- and *para*-rules, the structures of the two adducts could be tentatively assigned to be the keto aldehydes **42** and **43**. Previous observations indicated that the multiplicity and coupling pattern of the ring junction proton, H_8, could be used to determine the regiochemistry of the Diels-Alder adducts of 1-substituted dienes. Detailed ^1H decoupling experiments of the major isomer showed that irradiation of the dddd at δ 2.82 (H_8, J = 10.0, 8.0, 2.0, 2.0 Hz), led to a change in multiplicity of the signals at δ 2.47 (H_{11exo}), 2.10-2.30 (two protons, H_{7ax} and H_9) and 1.98 (H_{7e}). Like the previous cases, this coupling pattern indicated that two hydrogen atoms were attached to C_7 and consequently the methyl substituent must be at C_4 and confirmed the regiochemistry of the major isomer as shown by structure **42**.

To determine the stereochemistry of the ring junction and the C_4 methyl, NOE experiments were carried out with the major isomer. When proton H_8 (δ 2.82) was irradiated, a 5.8% enhancement on the *endo* methyl (δ 0.66) was observed. This indicated that the H_8 proton was on the same face as the *gem*-dimethyl group and therefore the addition of the diene occurred from the *Re*-face of **26**. The stereochemistry of the formyl group was then assigned in accordance with the *cis* principle. When the signal at δ 1.40 (C_4 methyl) was irradiated, NOE enhancements of 5.3% on H_5, 5.9% on H_4 and 6.4% on CHO were observed. This evidence confirmed the position and the stereochemistry of the methyl substituent as that specified by structure **42** for the major isomer.



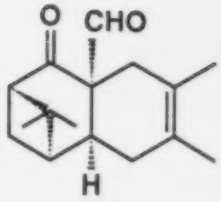
42

Figure 3. NOE data for adduct 42

The ^1H NMR spectral data of the minor isomer were incomplete. Therefore, we could not unambiguously assign the structure of the mnior isomer. The tentative assignment of structure **43** was based on the previous findings on a similar system.[84]

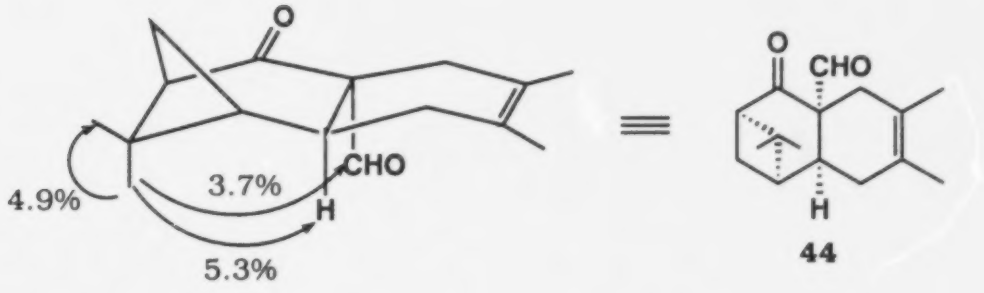
D. Addition to 2,3-dimethylbutadiene

Enone aldehyde **26** reacted with 2,3-dimethylbutadiene using boron trifluoride etherate as a catalyst to give a colourless liquid in 92% yield. It displayed a specific rotation of $[\alpha]^{23}_D$ +25.0° (c. 1.0, $CHCl_3$). The ^{13}C NMR spectrum indicated that the adduct was a single compound. The mass spectrum displayed a molecular ion peak at m/z 246.1619 ($C_{16}H_{22}O_2$). The IR spectrum showed bands at 1729 cm^{-1} due to a saturated aldehyde and at 1698 cm^{-1} due to a ketone. The ^1H NMR spectrum showed two broad singlets at δ 1.70 and 1.61 due to two vinylic methyls. The *gem*-dimethyl appeared as a pair of singlets at δ 1.31 and 0.71. The spectral data were consistent with the proposed structure **44**.



44

As in the preceding cases, the stereochemistry was determined on the basis of NOE experiments. Irradiation of the *endo* methyl at δ 0.71 resulted in NOE enhancements of 5.3% on H_8 (δ 2.88), 3.7% on CHO (δ 9.71) and 4.9% on *exo* methyl (δ 1.70). These findings supported the assigned stereochemistry of **44** resulting from the addition of the diene exclusively from the *Re*-face of enone aldehyde **26**.



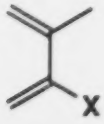
44

Figure 4. NOE data for adduct 44

E. Addition to 2-*tert*-butyldimethylsiloxy-3-methyl-1,3-butadiene

We were interested in introducing more functional groups into a Diels-Alder adduct to make the process more versatile. An oxygen containing diene **46** was chosen for this purpose. It was found in a previous study in our group[98] that a siloxy containing diene, like **45**

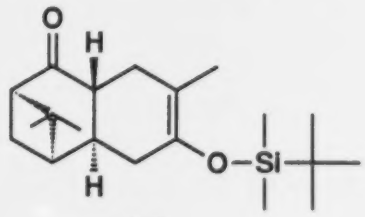
and **46**, is extremely sensitive to the acidity of a number of Lewis acids and only zinc chloride was useful to produce positive results. Thus, zinc chloride was chosen as the catalyst to affect the addition of 2-*tert*-butyldimethylsiloxy-3-methyl-1,3-butadiene (**46**) with **26**.



45 : X = OTMS; 46: X = OTBDMS

The reaction was found to be very fast, compared to other $ZnCl_2$ catalyzed Diels-Alder reactions in this series. The product was collected in 70% yield after purification by column chromatography on silica gel. Its ^1H NMR spectrum with $CDCl_3$ as a solvent gave a messy result. When the solution in the NMR tube was examined by TLC, two new spots appeared indicating that the adduct was an unstable compound and decomposed under acidic conditions. Thus, its NMR spectra were run in deuteriobenzene. The ^{13}C NMR spectrum showed that the adduct was a single compound. However, the signal corresponding to the aldehyde group was absent in both the ^1H and ^{13}C NMR spectra. The mass spectrum showed a molecular ion peak at m/z 334.2319 which was consistent with the formula of $C_{20}H_{34}O_2Si$. The IR spectrum displayed only one carbonyl band at 1715 cm^{-1}. The spectral evidence suggested that the formyl group was no longer present in the molecule. Other structrual features were present as expected for the Diels-Alder adduct. The ^1H NMR spectrum displayed a broad singlet at δ 1.43 for the vinylic methyl and two other methyl singlets at δ 1.01 and 0.89 (*gem*-dimethyl). It also displayed a singlet at δ 0.98 for *tert*-butyl and two singlets at δ 0.12 and 0.07 for the two

methyl groups on Si. The presence of a double bond was confirmed by the signals in the ^{13}C NMR spectrum at δ 140.95 (=C-O-) and 109.26 ($=CCH_3$).



46

Since the formyl group was eliminated during the reaction, the *cis*-principle could not be applied directly to the structure assignment. In addition, unlike other adducts in this series, several signals were unexpected down field in the ^1H NMR spectrum. Without extensive ^1H decoupling and NOE studies, a complete spectral assignment would not have been possible. To determine the regio- and stereochemistry of this adduct, NMR studies were carried out and the results are listed in Table 9.

Irradiation of the protons at δ 4.00, led to a change in multiplicity of the signals at δ 3.38 (H_{4ax}), 2.34 (H_{7ax}) and 1.43 (C_5-CH_3). When the signal at δ 3.31 (H_8) was irradiated, the signal at δ 3.38 was also irradiated due to their close proximity. As a result, changes of the multiplicity of the following signals at δ 4.00 (H_{4e}), 3.71 (H_3), 1.94 (H_9) and 1.43 (C_5-CH_3) were observed. Furthermore, irradiation of the proton at δ 2.29 (H_1), led to a change in multiplicity of the signals at δ

Table 9. ^1H NMR data for adduct **46**

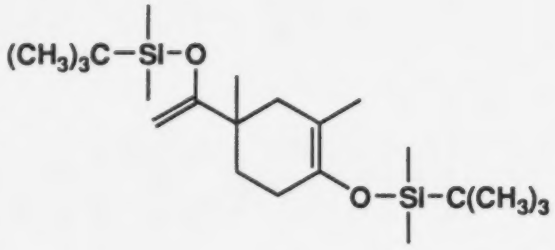
Proton	Chemical shift (δ ppm)	Multiplicity (J in Hz)
H_1	2.29	dd (6.0, 6.0)
H_{4ax}	3.38	dm (15.0)
H_{4e}, H_{7e}	4.00	m
H_3	3.71	dd (11.0, 3.5)
H_8	3.31	m
H_{7ax}	2.34	dm (15.0)
H_9	1.94	m
H_{11exo}	1.73	m
H_{11endo}	2.01	d (10.5)
vinylic CH_3	1.43	br s
$SiCH_3$	0.12	s
$SiCH_3$	0.07	s
$SiC(CH_3)_3$	0.98	s
exo CH_3	0.89	s
endo CH_3	1.01	s

1.94 (H_9) and 1.73 (H_{11exo}). These results made it clear that structure **46** expressed the correct regiochemistry of the adduct.

To determine the stereochemistry of the ring junction, NOE experiments were carried out and some very interesting results were obtained. From the spectral data obtained in this series, the methyl singlet at higher field, for this compound at δ 0.89, usually represented the *endo* methyl group. Therefore, we chose to irradiate the singlet at δ 0.89 to see if any NOE enhancement would occur on the ring junction protons. The results showed 16.5% enhancement on the signal at δ 2.29 (H_1), 10.2% on the signal at δ 1.94 (H_9) and 13% on the signal at δ 1.73 (H_{11exo}). It was very clear from these NOE results that the methyl singlet at δ 0.89 was due to the *exo* methyl. This result was different from the structural features of the other adducts in this series. The missing formyl group could cause the exchange of the chemical shifts between the two geminal methyl groups. We tried to irradiate proton H_8 at δ 3.31. Unfortunately, proton H_{4ax} at δ 3.38 was so close to H_8 that it was also irradiated and the results of this experiment did not prove to be constructive. Therefore, the stereochemistry of ring junction could not be determined by NOE experiments. On the other hand, the coupling pattern of the two protons at the ring junction positions and the large coupling constant (11 Hz) indicated a *trans* ring junction as depicted by structure **46**.

Since the diene used was in excess (10 eq) and its boiling point was high, 19.4% of the diene was recovered after column chromatography.

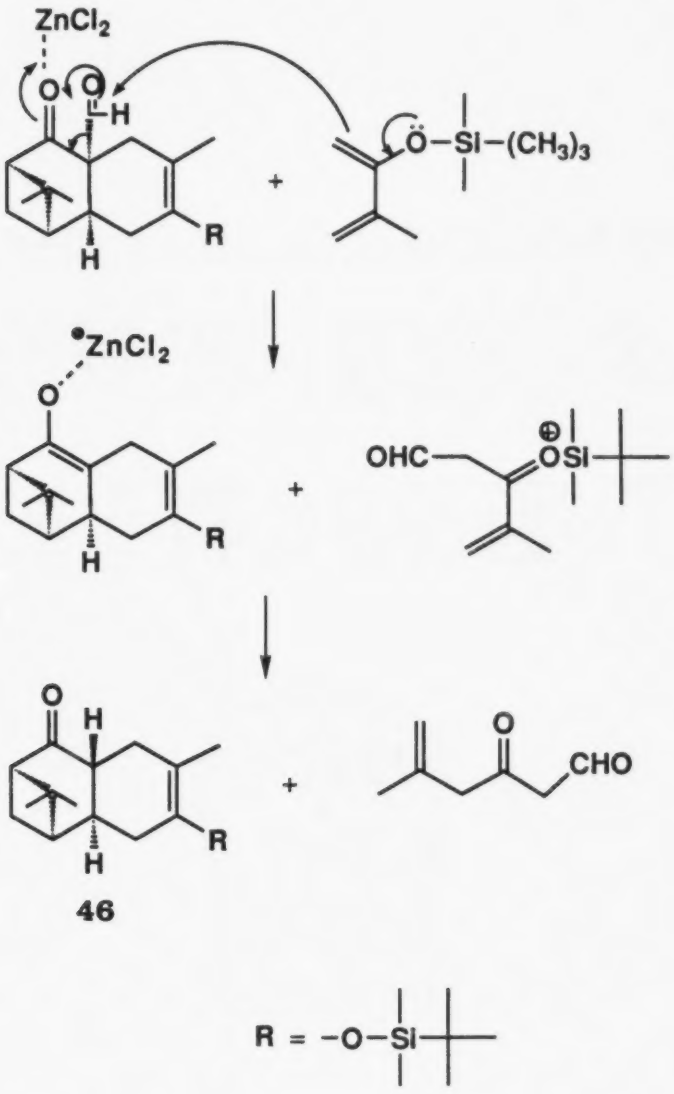
The Diels-Alder reaction of diene **46** itself also took place during the course of the reaction and 12% of the dimeric adduct was collected. This adduct showed two doublets (3 Hz each) at δ 4.20 and 4.18 for the terminal double bond protons, two singlets at δ 1.39 and 1.03 for the vinylic methyl and the allylic methyl, respectively, two singlets at δ 0.89 and 0.84 for the two *tert*-butyl groups and four singlets at δ 0.07, 0.09, 0.01 and 0.02 for the two dimethyl silyl moieties. The spectral data confirmed that the dimer could be expressed by structure **47**.



47

The spectral data of **46** suggested that this Diels-Alder adduct did not possess a formyl group. However, the question "When and how was the formyl group get lost?" remained to be answered. It could be eliminated during the reaction or during the workup after the addition of a saturated aqueous sodium bicarbonate solution. Another problem that we wanted to solve for this reaction was that a larger quantity of diene was used (due to the relatively high molecular weight of the diene), compared to the amount of diene used in other Diels-Alder additions in this series. Since this reaction was much faster than other zinc chloride catalyzed additions, there was a good possibility that the amount of diene could be reduced without lowering the yield.

Therefore we carried out this reaction again with 5 eq of 2-*tert*-butyldimethylsiloxy-3-methyl-1,3-butadiene. This time, the reaction



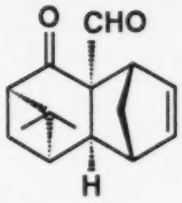
Scheme 10

was monitored in order to find out when the formyl group was removed. The reaction mixture was concentrated and the ^{1}H NMR

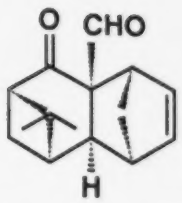
spectrum of the residue was recorded before the addition of the saturated sodium bicarbonate solution. The spectrum showed the disappearance of the formyl group, indicating its removal during the reaction. The yield was not affected by the deduction of the amount of the diene used. A possible mechanism for the elimination of the formyl group is outlined in Scheme 10.

F. Addition to 1,3-cyclopentadiene

Attempts to induce addition of 1,3-cyclopentadiene to **26** with boron trifluoride etherate as catalyst were fruitless, due to the rapid polymerization of the diene under the conditions. When a milder catalyst, zinc chloride, was used, the Diels-Alder reaction produced a mixture of two inseparable adducts in the ratio of 20:1 (by ^{1}H NMR) in 52% yield. The IR spectrum of this mixture showed absorptions at 1723 and 1694 cm^{-1}, indicating the presence of an aldehyde and a ketone, respectively. The mass spectrum showed a molecular ion peak at m/z 230.1308, corresponding to the formula $C_{15}H_{18}O_2$. The ^{1}H NMR displayed two sets of signals in an integral ratio of 20:1. The major set consisted of two doublets of doublets at δ 6.40 and 6.10, indicative of the presence of two vinylic protons. Singlets appeared at δ 1.32 and 0.82 for the *gem*-dimethyl group. The minor set displayed two vinylic protons at δ 6.21 and 6.10, each as a small broad peak whose multiplicity could not be recognized. The two singlets at δ 10.08 and 9.81 were attributed to the formyl group in the minor and major adduct, respectively.

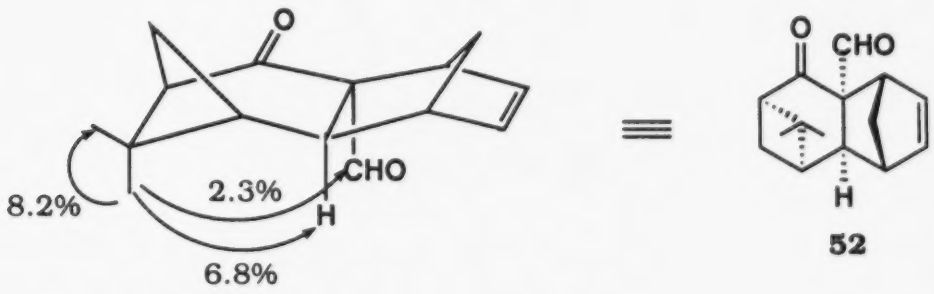


50



51

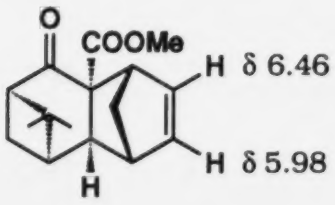
Preliminary analysis of the spectral data indicated that the structures of the adducts could be assigned as **50** and **51**. Extensive ^1H decoupling experiments on the major isomer led to the assignment of all its protons. The ring junction proton (H_8) appeared at δ 3.17 as a multiplet. Irradiation of the signals at δ 3.01 (H_7) and 2.30 (H_9) led to a small change in multiplicity of the signal at δ 3.17. In an NOE experiment, when the *endo* methyl at δ 0.80 of the major isomer was irradiated, a 6.8% enhancement on the signal at δ 3.17 and 2.3% on the signal at δ 9.81 as well as 8.2% on the signal at δ 1.32 were observed. Therefore, the major product was assigned with an α-H_8 and an α-formyl group.



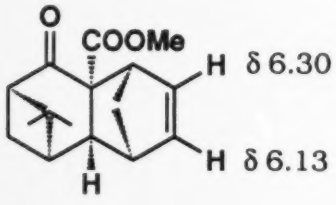
52

Figure 5. NOE data for adduct 52

Previous observations indicated that the addition of dienes to enone aldehyde occurred exclusively from the *Re*-face of **26**. It was therefore expected that exclusively addition of cyclopentadiene to the *Re*-face of **26** would also occur. Consequently, the minor isomer would most likely contain an α-H_8 and an α-formyl group as well.



52



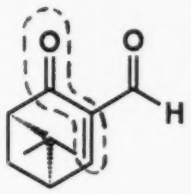
53

The stereochemistry of the methylene bridge of the bicyclo[2.2.1]heptene ring system was determined by comparing the difference in chemical shifts between the two vinylic protons with the known compounds **52** and **53**.[84] Since the major isomer exhibited a larger difference in chemical shift between the two vinylic protons (Δδ 0.30) than the minor isomer (Δδ 0.11), it was assigned to structure **50** accordingly, while the minor isomer was assigned to structure **51**.

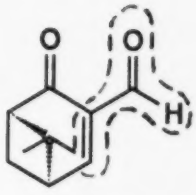
G. *endo*-Selectivity of the addition

An examination of the results in Table 5 reveals that the addition of dienes to enone aldehyde **26** proceeded with very high diastereomeric excess and a discussion of this *endo*-selectivity is required. As illustrated by structures **26b** and **26c**, there are in fact two dienophilic components in **26**: the α,β-unsaturated ketone (**26b**) and the α,β-unsaturated aldehyde (**26c**). Normally, it would be unnecessary to

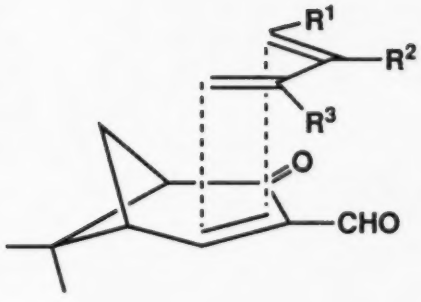
distinguish between these two moieties, except in certain cases where the *endo*-rule is in effect.



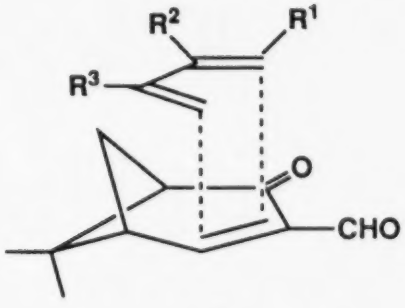
26b



26c



54



55

54a $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$

54b $R^1 = CH_3$, $R^2 = H$, $R^3 = H$

55a $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$

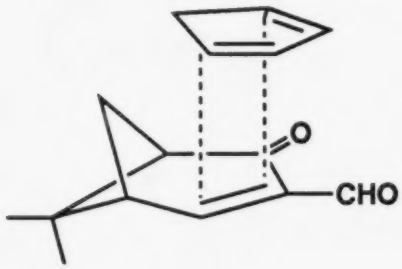
55b $R^1 = CH_3$, $R^2 = H$, $R^3 = H$

endo-Addition to the enone or to the α,β-unsaturated aldehyde moiety of **26** would give rise to stereochemically distinguishable products. The factor or factors determining which dienophilic moiety would dominate the reaction pathway is expected to be a function of the most effective secondary orbital overlap with the diene. It was observed that the addition of 1-substituted dienes (Table 5, Entries 1-3 and 9) to **26** occurred predominantly by secondary orbital overlap with the aldehyde (transition state **54**) rather than with the ketone

carbonyl (transition state **55**). Comparison between the two transition states indicates that the addition *via* transition state **55** would encounter some steric interaction between the C_2-C_3 of the diene and the methylene bridge of the dienophile.

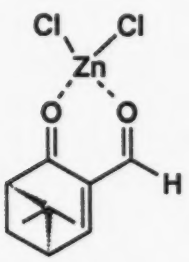
The addition of *trans*-2-methyl-1,3-pentadiene to **26** at -40 °C produced two C_4 epimeric adducts **42** and **43** in a ratio of 133:1. Keto aldehyde **42** would be the result of addition *via* transition state **54a** while **43** would be the result of addition *via* transition state **55a**. The preferential formation of adduct **42** can be attributed, at least in part, to the destablization of transition state **55a** by a steric interaction of the diene with the methylene bridge of the dienophile. On the other hand, addition *via* transition state **54a** would not encounter this steric interaction.

The cases of *trans*-piperylene (**37** and **38**) and cyclopentadiene (**50** and **51**) again showed high diastereoselectivity in favor of adducts **37** and **50** resulting from addition of dienes *endo* to the aldehyde group of **26** (transition state **54b** and **56**).

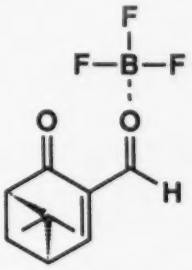


56

The electronic influence exerted by zinc chloride and boron trifluoride on the Diels-Alder additions of enone aldehyde **26** is probably ascribed to the bidentate complexation of $ZnCl_2$ with the β-dicarbonyl (**26d**) and the monodentate complexation of $BF_3 \cdot OEt_2$ mainly with the formyl group (**26e**).



26d



26e

H. Optical purity

After the Diels-Alder characteristics of enone aldehyde **26** were demonstrated, the optical purity of the Diels-Alder adducts was analyzed. (-)-β-Pinene used to prepare enone aldehyde **26** was obtained from Aldrich Chemical Co. and had an optical purity of 92%. Optically active NMR shift reagent, $Eu(hfc)_3$ has been used to evaluate the optical yield of reactions.[101,102] The direct application of $Eu(hfc)_3$ to adduct **35** showed a separation of the signals for the *gem*-dimethyl groups. The results obtained are summarized in Table 10. The $\Delta\delta$ increased with increasing amount of $Eu(hfc)_3$. In all experiments, the integrals of the split signals were consistently in the ratio of 96:4. This indicated that the optical purity of 92% was retained in the Diels-Alder adducts. Since both enantiomers of β-pinene are readily

available, one can prepare enantiomeric sets of Diels-Alder adducts with high optical purity.

Table 10. Splitting of methyl signals in the ^1H NMR spectrum (300 MHz) of adduct **35**

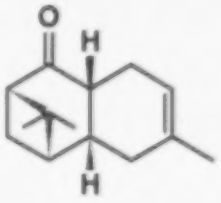
$Eu(hfc)_3$ (eq)	*endo* CH_3 ($\Delta\delta$)	*exo* CH_3 ($\Delta\delta$)
0.05	0.04	0.02
0.10	0.06	0.03
0.20	0.07	0.04

III. REMOVAL OF THE AUXILIARY GROUP

Having successfully generated various Diels-Alder adducts of enone aldehyde **26**, we wished to prove that a formyl group, as an effective anchor for controlling the stereoselectivity, is not only easily introduced, but also easily removed.

Treatment of **35** with saturated aqueous potassium carbonate in a methanol mixture at room temperature for 18 h afforded a single product in quantitative yield. This compound showed a specific rotation of $[\alpha]^{23}_D$ +107.5° (c. 1.77, $CHCl_3$) and a molecular ion peak at m/z 204.1511 in the mass spectrum indicating the formula $C_{14}H_{20}O$. The IR spectrum displayed a carbonyl absorption at 1713 cm^{-1}. The ^1H NMR spectrum showed a vinylic proton signal as a multiplet at δ 5.48 and a vinylic methyl as a broad singlet at δ 1.71. Methyl singlets also appeared at δ 1.38 and 0.79 (*gem*-dimethyl). The presence of a

ketone carbonyl (δ 214.83) and a double bond (δ 135.42 and 121.20) were confirmed by the ^{13}C APT NMR spectrum. The spectral data were found to be in good agreement with those previously reported for ketone **57** in our laboratory.

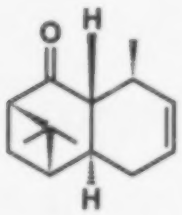


57

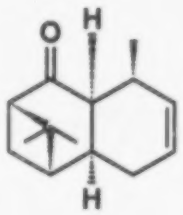
Treatment of the mixture of adducts **37** and **38** (64:1) under the same conditions for 18 h did not give any detectable amount of product. The starting material was recovered intact. However, after refluxing for 15 h, a colourless liquid was isolated in 92% yield. After chromatographic separation, two products in a ratio of 1:6 were obtained. The less polar minor isomer showed a molecular ion peak at m/z 204.1512 in the mass spectrum indicating the formula $C_{14}H_{20}O$. The IR spectrum displayed a carbonyl absorption at 1710 cm^{-1}. The ^1H NMR spectrum showed two vinylic protons as two multiplets at δ 5.55 and 5.49, a methyl as a doublet (J = 7.0 Hz) at δ 1.22. Methyl singlets also appeared at δ 1.37 and 0.78 (*gem*-dimethyl). The presence of a ketone carbonyl (δ 215.70) and a double bond (δ 135.27 and 129.96) were confirmed by the ^{13}C APT NMR spectrum.

The more polar major isomer displayed a molecular ion peak at m/z 204.1513 in the mass spectrum in agreement with the molecular formula $C_{14}H_{20}O$. In the IR spectrum an absorption at 1714 cm^{-1},

characteristic of a ketone carbonyl, was observed. The ^1H NMR[57] spectrum showed the vinylic proton signals as a doublet of multiplets at δ 5.63-5.77 and a methyl signal as a doublet (J = 7.0 Hz) at δ 1.10. Two singlets for the *gem*-dimethyl were observed at δ 1.36 and 0.87. The ^{13}C APT NMR spectrum displayed a signal in phase with $CDCl_3$ at δ 215.70, for a ketone carbonyl and two signals antiphase to $CDCl_3$ at δ 135.27 and 129.96 for a double bond.



59



60

Based on the spectral data, especially the ratio of the two products, structures **59** and **60** were assigned to the two compounds. We started with a 64:1 mixture of **37** and **38**. Mathematically, it is impossible that the minor product (in a 6:1 mixture) was from the minor starting material. The two deformylation products must be both derived from the major starting material and epimeric at C_3. The stereochemistry of C_3 remained to be determined. Extensive ^1H COSY experiments of the major isomer resulted in the assignment of all the protons. The ring junction proton, H_8, appeared at δ 2.71 as a multiplet. Its multiplicity changed when the following protons were irradiated individually: H_3 (δ 2.55), H_{11exo} (δ 2.40) and the multiplet at δ 1.98 - 2.20 (H_9, H_7 and other). In an NOE experiment, attempted irradiation of proton H_8 at δ 2.71 did not provide useful information.

since H_3 had also been irradiated. The ^1H NMR spectrum, however [58] showed proton H_3 as a doublet of doublets with coupling constants of 12.0 and 5.5 Hz. This large coupling constant (12 Hz) indicated that the major isomer had a *trans* ring junction while the minor isomer could be assigned as a *cis* ring junction.

IV. Conclusions

The Diels-Alder reaction of enone aldehyde **26** with various dienes provided good to high yields of chiral adducts in high diastereomeric excess with complete diastereofacial selectivity. The observed regiochemistry was as predicted by the *ortho*- and *para*-rules. Chemical transformations carried out on compound **57**[77] indicated that the Diels-Alder adducts discussed in this chapter are potentially useful in various synthetic schemes. In conclusion, enone aldehyde **26** has emerged as an efficient chiral reagent for asymmetric Diels-Alder reactions, and as a potentially useful precursor for many natural products.[84]

Experimental

General

Melting points were recorded on a Kofler hot stage apparatus and are not corrected. Combustion elemental analyses were performed by the microanalytical laboratory of this department. Fourier transform infrared spectra (FT-IR) were recorded on a Nicolet 7199 or Nicolet MX-1 FT-IR spectrophotometer and were normally obtained in chloroform cast unless otherwise stated. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker WH-80, Bruker WH-200, Bruker WH-300, Bruker WH-400 or Bruker AM-400 spectrometer using deuteriochloroform ($CDCl_3$) as solvent unless otherwise stated. Tetramethylsilane (TMS) was used as an internal reference. Coupling constants are reported to ± 0.5 Hz. Chemical shift measurements are reported in ppm downfield from TMS in delta (δ) units. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet and br. = broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker WH-300 (75 MHz) and Bruker WH-400 (125 MHz) spectrometer, and were obtained as solutions in deuteriochloroform as the internal standard setting the central peak at 77.00 ppm. ^{13}C APT NMR experiments were derived from Carr-Purcell-Meiboom-Gill spin echo J-modulated experiments (APT or Attached Proton Test).[103,104] Methyl and methine groups are shown as signals possessing an antiphase (a) with respect to the deuteriochloroform signal, whereas methylene groups, quaternary carbons and carbonyl groups appear in

phase (p) with it. Nuclear Overhauser Enhancement (NOE) experiments were determined in the difference mode in which a control (undecoupled) spectrum was computer subtracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals possessing antiphase with respect to the irradiated signal. Samples for NOE measurements were deoxygenated with argon gas for 10 min. High resolution electron impact mass spectra (HRMS) were recorded using an A.E.I. model MS-50 mass spectrometer. Chemical ionization mass spectra (CIMS) were recorded on an A.E.I. MS-12 mass spectrometer, using ammonia as the reagent gas. Spectral data are reported as m/z values. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Specific rotations, $[\alpha]_D$ are reported in degrees at the specified temperature and concentration (c.) is given in grams per 100 mL in the specified solvent. Bulb-to-bulb distillation was performed using a Kugelrohr distillation apparatus. Concentrations of solvent systems used in column chromatography are given by volumes, e.g. 20% ethyl acetate in petroleum ether means 20 parts of ethyl acetate by volume to 80 parts of petroleum ether by volume.

Materials

Unless otherwise stated, all materials used are commercially available. All reactions were carried out under a positive pressure of argon. Anhydrous reaction solvents were distilled under an argon atmosphere before use from the appropriate drying agents. Tetrahydrofuran (THF) was freshly distilled from a blue or purple solution of sodium and

benzophenone prior to use. Pyridine and dichloromethane were distilled from calcium hydride. Benzene and ether were distilled from lithium aluminum hydride. Reactions requiring anhydrous conditions were performed in oven or flame-dried glassware, assembled and allowed to cool while being purged with argon. The term *in vacuo* refers to solvent removal *via* Büchi rotatory evaporator at water aspirator pressure. Argon was passed through a column of 4 Å molecular sieves and a self indicating silica gel (coarse grained) as the indicator.

Flash chromatography developed by Still[105] was used routinely for purification and separation of product mixtures, using silica gel (Merck, 230-400 mesh). All solvents were distilled prior to use for chromatography. Analytical thin layer chromatography (TLC) was carried out on aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck, Darmstadt). Ultraviolet active materials were detected by visualization under a uv lamp (254 or 350 nm). For TLC, the visualization of the chromatograms was completed by dipping in an ethanol solution of vanillin (5%, w/v) and sulfuric acid (5%, v/v), followed by careful charring on a hot plate. Alternatively, an aqueous solution of phosphomolybdic acid (3%, w/v) containing ceric sulfate (0.5%,w/v) and sulfuric acid (3%, v/v) was used as the dipping solution, followed by charring on a hot plate.

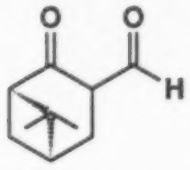
I. PREPARATION OF DIENOPHILE 26

(1R,5S)-(+)-6,6-Dimethylbicyclo[3.1.1]heptan-2-one (28)

At -78 °C, ozone was passed through a solution of (1S,5S)-(-)-β-pinene (10.0 g, 73.5 mmol) in 30 mL of mixed CH_2Cl_2 and MeOH (1:1). After 3.5 h, a persistant blue colour appeared. The reaction was stopped after another 40 min when the TLC showed no starting materal left. Excess ozone was purged with oxygen for 10 min, and the reaction mixture turned colourless. Dimethyl sulfide (27.5 mL, 0.37 mol) was added to the reaction mixture at -78 °C. Then the mixture was allowed to gradually warm up to room temperature while stirring overnight. The solvent was removed under reduced pressure on a rotary evapoartor. Flash chromatography of the residue on silica gel, eluting with 2-10% ether in petroleum ether, gave 7.2 g of pure **28** as a colourless oil. The second separation of the impure product by the same method gave another 2.2 g of **28** (total yield 9.4 g, 93%): $[\alpha]^{23}_D$ = + 15.0° (neat), + 29.6° (c, 1.32, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.64-2.47 (m, 3 H), 2.34 (ddd, 1 H, J= 19.0, 9.0, 2.5 Hz), 2.21 (m, 1 H), 2.10-1.87 (m, 2 H), 1.55 (d, 1 H, J= 10.0 Hz), 1.40 (s, 3 H, *exo* C**H**$_3$), 0.82 (s, 3 H, *endo* C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 214.97 (C=O), 58.04 (**C**HC=O), 41.24 (CMe_2), 40.47 (**C**HCMe_2), 32.84 (**C**H_2C=O), 25.95 (*exo* CH_3), 25.33 (CH_2), 22.16 (*endo* CH_3), 21.46 (CH_2); FT-IR 1708 cm^{-1} (C=O); HRMS M^+ 138.1046 (calcd. for

$C_9H_{14}O$: 138.1045). Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21; found: C, 78.06; H, 10.21.

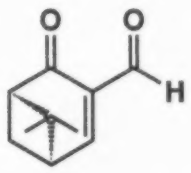
(1R,5R)-3-Formyl-6,6-dimethylbicyclo[3.1.1]hetpan-2-one (29)



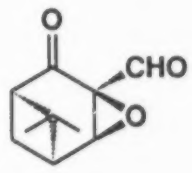
Sodium hydride (60% oil dispersion, 800 mg, 20.0 mmol) was suspended in THF (30 mL) under an atmosphere of argon. Ethyl formate (25 mL, 0.31 mol) was added at 0 °C and stirred for 10 min. A solution of 1.38 g (10.0 mmol) of nopinone (**28**) in 25 mL of THF containing 7 drops of 98% ethanol was added dropwise at 0 °C over a period of 30 min. Then the reaction mixture was allowed to gradually warm up to room temperature. After 3 h at room temperature, an aqueous solution of saturated ammonium chloride (25 mL) was added. The mixture was separated and the aqueous layer was extracted with a mixture of ether and petroleum ether (1:1, 3 x 20 mL). The combined organic layers were washed with water and saturated aqueous sodium chloride, dried with magnesium sulphate, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 5-10% ether in petroleum ether, gave keto aldehyde **29** (1.55 g, 9.34 mmol, 95% yield) as a colourless oil which solidified on standing. This compound existed as a 1:2.5:7 mixture of isomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.35 (br. s, 1 H, enol O**H**), 7.18 (br. s, 1 H, enol =C**H**), 2.41-

2.58 (m, 6 H), 1.41 (s, 3 H, *exo* C**H**$_3$), 0.90 (s, 3 H, *endo* C**H**$_3$); the other two minor isomers also showed some signals on the same NMR spectrum: δ 9.65, 9.40 (s, 1 H each, C**H**O), 1.44, 1.40 (s, 3 H each, *exo* C**H**$_3$), 0.93, 0.82 (s, 3 H each, *endo* C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 209.45 (C=O), 163.92 (CH=OH), 107.16 (C=), 54.14 (**C**HC=O), 39.56 (C), 39.40 (**C**HCMe$_2$), 27.49, 25.26 (2 x CH_2), 26.02, 21.48 (2 x CH_3); FT-IR 3310 cm^{-1} (enol OH), 1725 cm^{-1} (CHO), 1713 cm^{-1} (C=O), 1653 cm^{-1} (chelated β-hydroxy-α,β-unsaturated ketone carbonyl), 1598 cm^{-1} (C=C); HRMS M$^+$ 166.1009 (cacld. for $C_{10}H_{14}O_2$: 166.1004). Anal. Cacld. for $C_{10}H_{14}O_2$: C, 72.25; H, 8.49; found: C, 72.43; H, 8.73.

(1R,5R)-3-Formyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (26) and (1R,3R,5S,6R)-3-Formyl-7,7-dimethyl-4-oxatricyclo[4.1.1.0^{3,4}]-heptan-2-one (30)



26



30

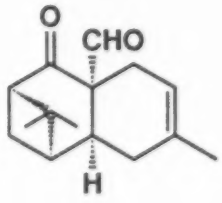
Pyridine (0.53 mL, 6.5 mmol) was added to a solution of phenylselenenyl chloride (1.37 g, 7.15 mmol) in dichloromethane (30 mL) at 0 °C under an argon atmosphere. After stirring for 10 min, keto aldehyde **29** (1.08 g, 6.5 mmol) in 10 mL of dichloromethane was added. After 5 min, the reaction mixture was washed with 1 N hydrochloride acid (2 x 30 mL). The organic layer was placed in a

flask and cooled to 0 °C. A 30% aqueous hydrogen peroxide solution (0.5 mL) was added dropwise. After stirring for 5 min, another 0.5 mL of 30% aqueous hydrogen peroxide was added. Another portion of aqueous hydrogen peroxide solution (15%, 1.0 mL) was added dropwise 7 min later. The resulting mixture was stirred for 1.5 h, water (5 mL) was added and the two layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 2-30% ether in petroleum ether gave a light yellow oil (746 mg) consisting of seven parts of enone aldehyde **26** (ca. 70% yield) and one part of epoxide **30**. The mixture showed the following spectral data: FT-IR 2830, 2710 cm^{-1} (CHO, weak), 1724, 1691, 1657 cm^{-1} (saturated and conjugated carbonyls), 1593 cm^{-1} (C=C); HRMS M^+ 164.0837 (cacld. for $C_{10}H_{12}O_2$: 164.0833), 180.0781 (cacld. for $C_{10}H_{12}O_3$: 180.0786); **26**: ^1H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1 H, C**H**O), 8.31 (dd, 1 H, =C**H**, J = 6.5, 1.5 Hz), 2.75-2.95 (m, 3 H, C**H**CH**H**$_{exo}$C**H**), 2.12 (d, 1 H, CH**H**$_{endo}$, J = 9.0 Hz), 1.57 (s, 3 H, *exo* C**H**$_3$), 1.02 (s, 3 H, *endo* C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 200.74 (C=O), 168.57 (CHO), 165.42 (CH=), 132.25 (C=), 58.35 (**C**HC=O), 54.82 (C), 44.74 (**C**HCMe$_2$), 40.38 (CH_2), 26.62, 21.48 (2 x CH_3); **30**: ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1 H, C**H**O), 3.87 (d, 1 H, CHC**H**-O, J = 4.5 Hz), 2.69 (dd, 1 H, CH**H**$_{exo}$, J = 11.0, 6.0 Hz), 2.55 (dd, 1 H, C**H**C=O, J = 6.0, 6.0 Hz), 2.33 (ddd, 1 H, C**H**CMe$_2$, J = 11.0, 6.0, 4.5 Hz), 2.06 (dd, 1 H, CHC**H**$_{endo}$, J = 11.0, 11.0 Hz), 1.45 (s, 3 H, *exo* C**H**$_3$), 1.05 (s, 3 H, *endo* C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 194.69 (CHO), 58.60 (CH), 56.70 (**C**HC=O), 40.68 (**C**HCMe$_2$), 26.53, 21.13 (2 x CH_3), 20.39 (CH_2).

Epoxide **30** was recovered in pure form from the Diels-Alder reaction mixture after **26** was totally consumed. It showed following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1 H, C**H**O), 3.89 (d, 1 H, CHC**H**-O, J = 4.5 Hz), 2.71 (dd, 1 H, CH**H**$_{exo}$, J = 11.0, 6.0 Hz), 2.58 (dd, 1 H, C**H**C=O, J = 6.0, 6.0 Hz), 2.38 (ddd, 1 H, C**H**Me_2, J = 11.0, 6.0, 4.5 Hz), 2.09 (dd, 1 H, CHC**H**$_{endo}$, J = 11.0, 11.0 Hz), 1.49 (s, 3 H, *exo* C**H**$_3$), 1.09 (s, 3 H, *endo* C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 201.80 (C=O), 194.69 (CHO), 58.90 (CH), 56.73 (**C**HC=O), 49.98 (C), 40.72 (**C**HMe_2), 26.55, 21.14 (2 x CH_3), 20.68 (CMe_2), 20.41 (CH_2); FT-IR 1741 cm^{-1} (CHO), 1710 cm^{-1} (C=O), 1100 cm^{-1} (C-O); HRMS M^++1 181.0863 (cacld. for $C_{10}H_{12}O_3$: 181.0865).

II. DIELS-ALDER REACTIONS OF ENONE ALDEHYDE 26

(1R,3R,8S,9R)-(-)-3-Formyl-6,10,10-trimethyltricyclo[7.1.1.0^{3,8}]-undec-5-en-2-one (35)



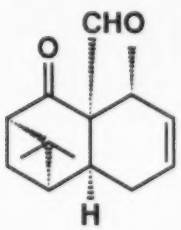
To a solution of a mixture of **26** and **30** (100 mg, **26**:**30** = 9:1), isoprene (0.54 mL, 5.4 mmol, 10 eq) in ether (7 mL) was added at -20 °C under an argon atmosphere, followed by the addition of boron trifluoride etherate (0.07 mL, 0.54 mmol). After stirring for 1 h and

45 min, a saturated aqueous $NaHCO_3$ solution (7 mL) was added. The mixture was separated and the aqueous layer was extracted with ether (3 x 7 mL). The combined organic layers were washed with water and brine, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 2-30% ether in petroleum ether, gave **35** as colourless oil (105.2 mg, 84% yield): $[\alpha]^{23}_D$ = -115.87° (c. 0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1 H, C**H**O), 5.33 (m, 1 H, C**H**=), 2.94 (dddd, 1 H, CHC**H**CH_2, J = 10.0, 7.5, 2.0, 2.0 Hz), 2.83 (dd, 1 H, CH**H**$_{ax}$CH=, J = 16.0, 7.0 Hz), 2.61 (dd, 1 H, C**H**C=O, J = 5.5, 5.5 Hz), 2.52 (dddd, 1 H, CHC**H**$_{exo}$H, J = 11.0, 8.5, 5.5, 2.0 Hz), 2.22 (dddd, 1 H, C**H**$_e$HCH=, J = 16.0, 8.0, 2.5, 2.5 Hz), 2.15 (m, 2 H, C**H**CMe_2, C**H**$_e$HC=), 1.91 (m, 1 H, CH**H**$_{ax}$C=), 1.89 (d, 1 H, CH**H**$_{endo}$, J = 11.0 Hz), 1.74 (br. s, 3 H, C**H**$_3$C=), 1.32 (s, 3 H, *exo* C**H**$_3$), 0.73 (s, 3 H, *endo* C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 212.94 (C=O), 200.86 (CHO), 139.76 (CH_3**C**=), 116.38 (CH=), 68.22 (C), 61.92 (C), 57.49 (**C**H), 47.83 (CH), 33.41, 33.03 (2 x CH_2), 30.42 (CH), 26.47 (=C**C**H_3), 25.27 (CH_2), 23.15, 21.74 (2 x CH_3); FT-IR 1730 cm^{-1} (CHO), 1698 cm^{-1} (C=O), 1600 cm^{-1} (C=C); HRMS M^+ 232.1462 (cacld. for $C_{15}H_{20}O_2$: 232.1464). Anal. Cacld. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; found: C, 77.43; H, 8.94.

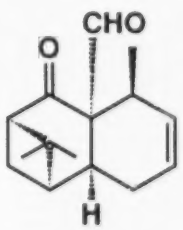
The Diels-Alder reactions of enone aldehyde **26** with isoprene using $FeCl_3$ and $SnCl_4$ as catalysts were carried out according to the general procedure illustrated above. Temperatures and times can be found in Table 5.

The procedure of $ZnCl_2$ catalyzed reactions was slightly different from that of boron trifluoride catalyzed reactions. An example of the procedure of $ZnCl_2$ catalyzed reactions is as follows. $ZnCl_2$ (91.4 mg, 0.67 mmol, 1 eq) was flame-dried ans dissolved in ether (5 mL) at room temperature under an atmosphere of argon. A solution of a mixture of **26** and **30** (110 mg, 10:1, 0.60 mmol of **26**) in ether (2 mL) was added dropwise. After stirring for 10 min, the reaction mixture was cooled to -20 °C and then isoprene (0.7 mL, 6.7 mmol, 10 eq) was added. The workup procedure was the same as that described above.

(1R,3R,4R,8S,9R)- (37) and (1R,3R,4S,8S,9R)-3-Formyl-4,10,10-trimethyltricyclo[7.1.1.$0^{3,8}$]undec-5-en-2-one (38)



37

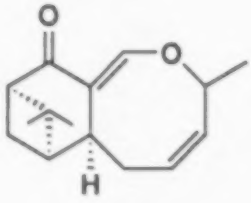


38

After the reaction (with boron trifluoride etherate catalysis) was completed, flash chromatography of the residue on silica gel with 0-10% ether in petroleum ether gave a mixture of **37** and **38** (in the ratio of 64:1 respectively): FT-IR 1723 cm^{-1} (CHO), 1693 cm^{-1} (C=O); HRMS M^+ 232.1461 (cacld. for $C_{15}H_{20}O_2$: 232.1463). Anal. Cacld. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; found: C, 77.30; H, 8.77; the NMR spectra showed two sets of signals; the major set for **37**: ^1H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1 H, C**H**O), 6.00 (m, 1 H, C**H**=), 5.42 (ddd, 1

H, =C**H**, J = 9.5, 3.0, 3.0 Hz), 2.80 (dddd, 1 H, CHC**H**CH_2, J = 10.5, 7.5, 2.0, 2.0 Hz), 2.62 (dd, 1 H, C**H**C=O, J = 5.5, 5.5 Hz), 2.58 (m, 1 H, CH_3C**H**CH=), 2.48 (dddd, 1 H, CH**H**$_{exo}$, J = 11.0, 5.5, 5.5, 2.0 Hz), 2.34 (ddd, 1 H, C**H**$_e$HCH=, J = 15.0, 7.5, 7.5 Hz), 2.10 (ddd, 1 H, C**H**Me_2, J = 5.5, 5.5, 2.0 Hz), 1.89 (d, 1 H, CH**H**$_{endo}$, J = 11.0 Hz), 1.85 (m, 1 H, CH**H**$_{ax}$CH=), 1.40 (d, 3 H, C**H**$_3$CH, J = 7.5 Hz), 1.31 (s, 3 H, *exo* C**H**$_3$), 0.71 (s, 3 H, *endo* C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 211.0 (C=O), 204.27 (CHO), 130.88, 127.91 (CH=CH), 68.26 (CH), 57.65 (CH), 56.20 (CH), 50.32 (C),41.90 (CMe_2), 39.72 (CH), 32.45 (CH_3), 28.09 (CH_2), 26.33 (CH_3), 24.19 (CH_2), 21.43 (CH_3); the minor set for **38**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1 H, C**H**O), 6.00 (m, 1 H, C**H**=), 5.75 (dddd, 1 H, =C**H**, J = 9.5, 6.0, 1.5, 1.5 Hz), 3.0 (m, 1 H, CHC**H**CH_2), 2.88 (ddd, 1 H, CH_3C**H**CH=, J = 14.0, 7.0, 7.0 Hz), 2.20 (ddd, 1 H, C**H**HCH=, J = 15.5, 7.0, 7.0 Hz), 2.03 (ddd, 1 H, C**H**Me_2, J = 6.0, 6.0, 2.5 Hz), 1.32 (s, 3 H, *exo* C**H**$_3$), 1.05 (d, 3 H, C**H**$_3$C=, J = 7.0 Hz), 0.66 (s, 3 H, *endo* C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 131.08, 128.35 (CH=CH), 71.52 (CH), 57.22 (CH), 48.10 (CH_3), 40.71 (CH), 26.71 (CH_3), 26.50 (CH_2), 20.79 (CH_2), 19.11 (CH_3).

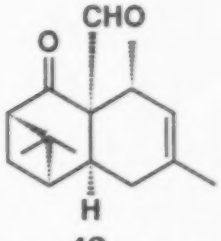
(1R,10S,11R)-6,12,12-trimethyl-5-oxatricyclo[9.1.1.0^{3,10}]undeca-3,7-dien-2-one (39)



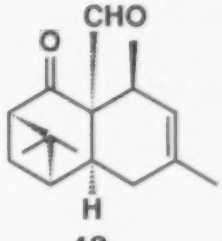
39

Compound **39** (colourless crystals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1 H, =C**H**-O), 5.82 (m, 1 H, C**H**=), 5.53 (dddd, 1 H, =C**H**, J = 15.5, 7.0, 7.0, 1.5 Hz), 4.59 (dddd, 1 H, O-C**H**Me, J = 7.5, 7.0, 3.0, 1.5 Hz), 2.81 (ddd, 1 H, CHC**H**CH_2, J = 12.0, 4.5, 2.0 Hz), 2.36-2.50 (m, 2 H, C**H**$_2$CH=), 2.10 (dd, 1 H, C**H**C=O, J = 5.5, 5.5 Hz), 1.73 (m, 3 H, C**H**$_2$C**H**), 1.39 (d, 3 H, CHC**H**$_3$, J = 7.5 Hz), 1.35 (s, 3 H, C**H**$_3$), 0.95 (s, 3 H, C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 203.78 (C=O), 151.77 (=CH-O), 129.82, 129.63 (CH=CH), 113.01 (C=), 79.07 (CH), 56.32(CH), 43.23 (CH), 40.95 (C), 32.44 (CH), 31.37 (CH_2), 26.55 (CH_3), 24.16 (C), 21.50, 17.78 (2 x CH_3); FT-IR 1684 cm^{-1} (C=O), 1602 cm^{-1} (C=C); HRMS M$^+$ 232.1462 (cacld. for $C_{15}H_{20}O_2$: 232.1463).

(1R,3R,4R,8S,9R)- (42) and (1R,3R,4S,8S,9R)-3-Formyl-4,6,10,10-tetramethyltricyclo[7.1.1.0^{3,8}]undec-5-en-2-one (43)



42

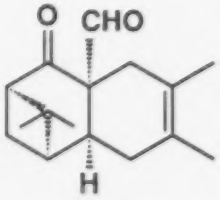


43

Compounds **42** and **43** were obtained as a 133:1 mixture (colourless oil) after flash chromatography: FT-IR 1713 cm^{-1} (CHO), 1694 cm^{-1} (C=O); HRMS M$^+$ 246.1619 (cacld. for $C_{16}H_{22}O_2$: 246.1619); the NMR spectra displayed two sets of signals. The major set for **42**: ^{1}H NMR

(300 MHz, $CDCl_3$) δ 10.04 (s, 1 H, C**H**O), 5.08 (m, 1 H, =C**H**), 2.82 (dddd, 1 H, CHC**H**CH_2, J = 10.0, 8.0, 2.0, 2.0 Hz), 2.61 (dd, 1 H, C**H**C=O, J = 5.5, 5.5 Hz), 2.56 (m, 1 H, CH_3C**H**CH=), 2.47 (m, 1 H, CH**H**$_{exo}$), 2.10-2.30 (m, 2 H, CH**H**$_e$C=, C**H**CMe_2), 1.98 (dm, 1 H, C**H**$_{ax}$HC=, J = 14.5 Hz), 1.90 (d, 1 H, CH**H**$_{endo}$, J = 11.0 Hz), 1.78 (br. s, 3 H, C**H**$_3$C=), 1.41 (d, 3 H, CHC**H**$_3$, J = 7.5 Hz), 1.32 (s, 3 H, *exo* C**H**$_3$), 0.66 (s, 3 H, *endo* C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 211.90 (C=O), 204.23 (CHO), 138.47 (C), 124.58 (CH=), 64.15 (C), 55.77 (CH), 48.01 (CH), 42.04 (CMe_2), 40.26 (CH), 33.49 (CH_2), 32.43 (CH), 26.37 (CH_3), 24.13 (CH_2), 22.77, 21.41 (2 x CH_3), 16.18 (CH_3); the minor set for **43**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1 H, C**H**O), 5.37 (m, 1 H, C**H**=), 3.05 (m, 1 H, CHC**H**CH_2), 2.93 (dd, 1 H, C**H**C=O, J = 7.5, 7.5 Hz), 1.89-2.00 (m, 3 H), 1.82 (d, 1 H, CH**H**$_{endo}$, J = 10.5 Hz), 1.73 (br. s, 3 H, C**H**$_3$C=), 1.33 (s, 3 H, *exo* C**H**$_3$), 1.20 (d, 3 H, CHC**H**$_3$, J = 7 Hz), 1.02 (s, 3 H, *endo* C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 129.40 (C=), 123.60 (CH=), 61.58 (C), 57.27 (CH), 41.50 (CH), 31.50 (CH_2), 26.81 (CH_3), 23.10 (CH_3), 21.04 (CH_3), 20.69 (CH_2), 18.77 (CH_3).

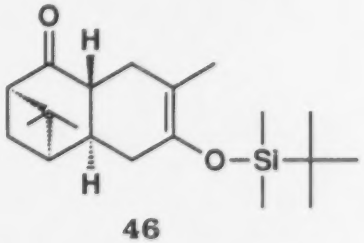
(1R,3R,8S,9R)-(+)-3-Formyl-5,6,10,10-tetramethyltricyclo[7.1.1.0^{3,8}]-undec-5-en-2-one (44)



44

Adduct **44** (colourless oil): $[\alpha]^{23}_D$ = + 25.0° (c. 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1 H, C**H**O), 2.88 (dddd, 1 H, CHC**H**CH_2, J = 10.5, 6.0, 2.0, 2.0 Hz), 2.67 (d, 1 H, CCH**H**$_{ax}$C=, J = 15.0 Hz), 2.61 (dd, 1 H, C**H**C=O, J = 5.5, 5.5 Hz), 2.51 (dddd, 1 H, CHC**H**$_{exo}$, J = 11.0, 6.0, 5.5, 2.0), 2.33 (br. d, 1 H, CC**H**$_e$HC=, J = 15.0 Hz), 1.97-2.17 (m, 3 H, CHC**H**HC=, CHCH**H**C=, C**H**CMe_2), 1.86 (d, 1 H, CH**H**$_{endo}$, J = 11 Hz), 1.70, 1.61 (br. s, 2 x 3 H, 2 x C**H**$_3$C=), 1.31 (s, 3 H, *exo* C**H**$_3$), 0.71 (s, 3 H, *endo* C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 213.45 (C=O), 200.56 (CHO), 130.00 (CH_3**C**=), 122.71 (CH_3**C**=), 62.96 (C), 57.53 (CH), 47.51 (CH), 41.33 (C), 39.90 (CH_2), 34.69 (CH_2), 30.19 (CH), 26.48 (CH_3), 25.11 (CH_2), 21.71 (CH_3), 19.14, 18.99 (2 x CH_3); FT-IR 1729 cm^{-1} (CHO), 1698 cm^{-1} (C=O); HRMS M^+ 246.1619 (cacld. for $C_{16}H_{22}O_2$: 246.1619). Anal. Cacld. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00; found: C, 77.95; H, 8.87.

(1R,3R,8S,9R)-6-(*tert*-butyldimethylsiloxy)-5,10,10-trimethyltricyclo-[7.1.1.0^{3,8}]undec-5-en-2-one (46)

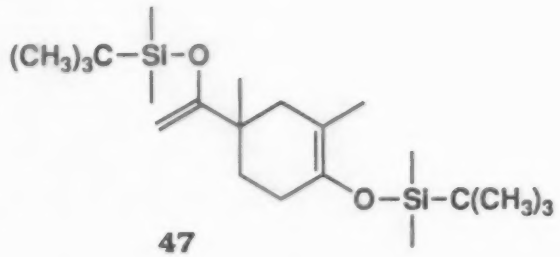


46

Ketone **46** (colourless oil): ^1H NMR (300 MHz, C_6D_6) δ 4.00 [m, 2 H, CH**H**$_e$(CH_3)C=, CH**H**$_e$COSi], 3.71 (dd, 1 H, O=CC**H**CH_2, J = 11.0, 3.5 Hz), 3.38 (dm, 1 H, C**H**$_{ax}$H(CH_3)C=, J = 15.0 Hz), 3.31 (m, 1 H,

CHC**H**CH_2), 2.34 (dm, 1 H, C**H**$_{ax}$HCOSi, J = 15.0 Hz), 2.29 (dd, 1 H, C**H**C=O, J = 6.0, 6.0 Hz), 2.01 (d, 1 H, CH**H**$_{endo}$, J = 10.5 Hz), 1.94 (m, 1 H, C**H**CMe_2), 1.73 (m, 1 H, CH**H**$_{exo}$), 1.43 (br. s, 3 H, C**H**$_3$C=), 1.01 (s, 3 H, *endo* C**H**$_3$), 0.98 [s, 9 H, C(C**H**$_3$)$_3$], 0.89 (s, 3 H, *exo* C**H**$_3$), 0.07, 0.12 [s, 3 H each, 2 x Si(C**H**$_3$)$_2$]; ^{13}C APT NMR (75 MHz, C_6D_6) δ 204.22 (C=O), 140.95 (=C-OSi), 109.26 (CH_3**C**=), 75.74 (CH), 69.31 (CH_2), 58.60 (CH), 58.16 (C), 57.58 (CH), 49.04 (C), 40.88 (CH), 32.18 (CH_2), 34.69 (CH_2), 26.48 (CH_3), 25.11 21.71 (CH_3), 19.14, 18.99 (2 x CH_3); FT-IR 1715 cm^{-1} (C=O); HRMS M^+ 334.2324 (cacld. for $C_{20}H_{34}O_2Si$: 334.2328).

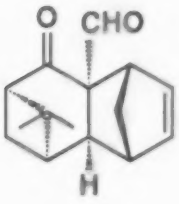
1-(*tert*-butyldimethylsiloxy)-4-[1-(*tert*-butyldimethylsiloxy)ethenyl]-2,4-dimethylcyclohexene (47)



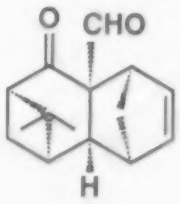
47

Compound **47** (colourless oil): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (d, 1 H, =C**H**H, J = 3.0 Hz), 4.18 [d, 1 H, =CH**H**, J = 3.0 Hz), 1.39 (s, 3 H, C**H**$_3$C=), 1.30 (m, 6 H), 1.03 (s, 3 H, CC**H**$_3$), 0.89 [s, 9 H, C(C**H**$_3$)$_3$], 0.84 [s, 9 H, C(C**H**$_3$)$_3$], 0.09, 0.07 [s, 3 H each, Si(C**H**$_3$)$_2$], 0.02, 0.01 [s, 3 H each, Si(C**H**$_3$)$_2$].

(1R,3R,4S,7R,8S,9R)- (50) and (1R,3R,4R,7S,8S,9R)-3-Formyl-10,10-dimethyltetracyclo[7.1.1.1.^{4,7}0^{3,8}]dodec-5-en-2-one (51)



50

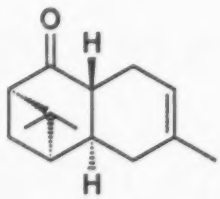


51

The two inseparable products (as colourless oil) showed the following spectral data: FT-IR 1723 cm^{-1} (CHO), 1694 cm^{-1} (C=O); HRMS M^+ 230.1308 (calcd. for $C_{15}H_{18}O_2$: 230.1307). The NMR spectra exhibited two sets of signals: the major set for **50**: ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1 H, C**H**O), 6.40 (dd, 1 H, CHCHC**H**=, J = 5.5, 3.0 Hz), 6.10 (dd, 1 H, CCHC**H**=, J = 5.5, 3.0 Hz), 3.33 (m, 1 H, CHC**H**CH=), 3.17 (m, 1 H, CHC**H**CH), 3.01 (br. s, 1 H, CC**H**CH=), 2.42 (d, 1 H, CH**H**$_{endo}$, J = 12.0 Hz), 2.36 (dd, 1 H, C**H**C=O, J = 6.6, 6.0 Hz), 2.19-2.35 (m, 2 H, C**H**$_{exo}$H, CH_2C**H**CH), 1.70 (br. d, 1 H, CHCH**H**CH, J = 8.5 Hz), 1.32 (s, 3 H, *exo* C**H**$_3$), 1.27 (ddd, 1 H, CHC**H**HCH, J = 8.5, 4.0, 2.0 Hz), 0.82 (s, 3 H, *endo* C**H**$_3$); ^{13}C APT NMR (125 MHz, $CDCl_3$) δ 217.70 (C=O), 199.90 (CHO), 142.31, 134.01 (CH=CH), 68.21 (C), 65.90 (C), 57.80 (CH), 52.34 (CH), 48.25 (CH), 47.21 (CH_2), 45.37 (CH), 39.10 (CH), 27.00 (CH_3), 22.44 (CH_2), 15.32 (CH_3); the minor set for **51**: ^1H NMR (300 MHz, $CDCl_3$) δ 10.08 (s, 1 H, C**H**O), 6.21 (m, 1 H, C**H**=), 6.10 (m, 1 H, C**H**=), 1.31 (s, 3 H, CH_3), 0.81 (s, 3 H, CH_3); ^{13}C APT NMR (125 MHz, $CDCl_3$) δ 130.92, 128.85 (CH=CH), 71.60 (C), 43.27 (C), 38.80 (CH), 30.42 (CH_2), 28.98 (CH_2), 14.09, 11.01 (2 x CH_3).

III. REMOVAL OF THE AUXILIARY GROUP

(1R,3R,8S,9R)-(-)-6,10,10-Trimethyltricyclo[7,1,1,$0^{3,8}$]undec-5-en-2-one (57)

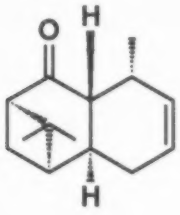


57

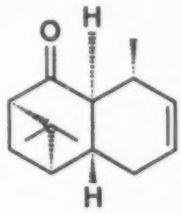
Keto aldehyde **35** (70 mg, 0.30 mmole) was dissolved in methanol (10 mL). A saturated aqueous potassium carbonate solution (10 mL) was added. After stirring for 18 h at room temperature, the reaction mixture was extracted with a solution of ether and petroleum ether (1 : 1; 10 mL x 3). The combined organic layers were washed with water and brine, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel. Elution with 0-3% ether in petroleum ether afforded **57** (60 mg, 0.295 mmol, 98% yield): $[\alpha]^{23}D$ = -47.7° (c. 2.286, $CHCl_3$); m.p. 53-54 °C (crystalization from petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 5.48 (br. s, 1 H, =C**H**), 2.60 (dd, 1 H, C**H**C=O, J = 5.0, 5.0 Hz), 2.30-2.50 (m, 3 H), 1.83-2.20 (m, 6 H), 1.71 (br. s, 3 H, =CC**H**$_3$), 1.38 (s, 3 H, *exo* C**H**$_3$), 0.79 (s, 3 H, *endo* C**H**$_3$); ^{13}C APT NMR (125 MHz, $CDCl_3$) δ 214.83 (C=O), 135.42 (=C), 121.20 (=CH), 58.57 (CH), 46.40 (CH), 45.02 (CH), 44.70 (C), 36.60 (CH_2), 36.54 (CH), 26.80 (CH_3), 25.02, 24.06

(2 x CH_2), 23.72, 21.96 (2 x CH_3); FT-IR 1713 cm^{-1} (C=O); HRMS M^+ 204.1511 (cacld. for $C_{14}H_{20}O$: 204.1514); Anal. Cacld. for $C_{14}H_{20}O$: C, 82.29; H, 9.87; found: C, 82.04; H, 9.97.

(1R,3R,4R,8S,9R)- (59) and (1R,3S,4R,8S,9R)-4,10,10-Trimethyltricyclo[7,1,1,$0^{3,8}$]undec-5-en-2-one (60)



59



60

A mixture of keto aldehydes **37** and **38** (45.0 mg, 0.194 mmole, 64:1) was dissolved in methanol (20 mL). A saturated aqueous potassium carbonate solution (20 mL) was added. After refluxing for 15 h, the reaction mixture was cooled to room temperature and extracted with a solution of ether and petroleum ether (1:1; 15 mL x 3). The combined organic layers were washed with water and brine, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel. Elution with 0-3% ether in petroleum ether afforded **60** (5.2 mg, 0.025 mmol, 13.1% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 5.55 (m, 1 H, =C**H**), 5.49 (m, 1 H, C**H**=), 2.60 (dd, 1 H, C**H**C=O, J = 5.0, 5.0 Hz), 2.30-2.45 (m, 3 H), 2.00-2.15 (m, 4 H), 1.70 (d, 1 H, CH**H**$_{endo}$, J = 11.0 Hz), 1.37 (s, 3 H, *exo* C**H**$_3$), 1.22 (d, 3 H, CHC**H**$_3$, J = 7.0 Hz), 0.78 (s, 3H, *endo* C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 215.70 (C=O), 135.27, 129.96 (CH=CH), 59.23 (CH), 52.60

(CH), 45.26 (CH), 45.00 (C), 36.29 (CH), 31.56 (CH_2), 30.11 (CH), 26.78 (CH_3), 24.19 (CH_2), 21.49, 16.04 (2 x CH_3); FT-IR 1710 cm^{-1} (C=O); HRMS M^+ 204.1512 (cacld. for $C_{14}H_{20}O$: 204.1514).

Continued elution gave **59** (31.2 mg, 0.153 mmole) in 78.8% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 - 5.63 (m, 2 H, C**H**=C**H**), 2.71 (m, 1 H, CHC**H**CH_2), 2.64 (dd, 1 H, C**H**C=O, J = 5.0, 5.0 Hz), 2.55 (dd, 1 H, O=CC**H**CH, J = 12.0, 5.5 Hz), 2.40 (m, 1 H, C**H**$_{exo}$H), 1.98 - 2.20 (m, 4 H, C**H**CMe_2, C**H**HCH=, CH**H**CH=, MeC**H**CH=), 1.82 (d, 1 H, CH**H**$_{endo}$, J = 11 Hz), 1.36 (s, 3 H, *exo* C**H**$_3$), 1.10 (d, 3 H, CHC**H**$_3$, J = 7.0 Hz), 0.87 (s, 3 H, *endo* C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 214.57 (C=O), 134.26, 126.04 (CH=CH), 58.48 (CH), 49.36 (CH), 45.09 (CH), 44.47 (C), 32.33 (CH), 31.54 (CH_2), 29.86 (CH), 27.23 (CH_3), 24.36 (CH_2), 21.49, 15.53 (2 x CH_3); FT-IR 1714 cm^{-1} (C=O); HRMS M^+ 204.1513 (cacld. for $C_{14}H_{20}O$: 204.1514).

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